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TITLE OF THE INVENTION (280 characters max)

KINASE INHIBITORS

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25885

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Respectfully submitted,
SIGNATURE

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47,145

☐ Additional inventors are being named on separately numbered sheets attached hereto

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KINASE INHIBITORS

BACKGROUND OF THE INVENTION

The p38 kinase is a mitogen-activated protein (MAP) kinase that belongs to the serine/threonine kinase superfamily. This kinase is activated by extracellular stresses such as heat, UV light, and osmotic stress, as well as by inflammatory stimuli such as lipopolysaccharide. When activated, p38 kinase phosphorylates intracellular protein substrates that regulate the biosynthesis of the pro-inflammatory cytokines tumor necrosis factor α (TNF- α) and interleukin-1 β (IL-1 β). These cytokines are implicated in the pathology of a number of chronic inflammatory disorders (Lee, et al., Ann. N.Y. Acad. Sci., **696**, 149-170 (1993); Muller-Ladner, Curr. Opin. Rheumatol., **8**, 210-220 (1996)), cardiovascular and central nervous system disorders (Salituro, et al., Current Medicinal Chemistry, **6**, 807-823 (1999)), and autoimmune disorders (Pargellis, et al., Nature Structural Biology, **9**(4), 268-272 (2002)).

A number of compounds within the pyridinylimidazole (WO9621452, WO9725045, US5656644, US5686455, US5717100, WO9712876, WO9821957, WO9847892, WO99903837, WO9901449, WO0061576, WO0172737) and pyrimidinylimidazole (WO9725048, WO9901452, WO9725046, WO9932121, WO9901131, WO9901130, WO9901136, WO9807452, WO9747618, WO9856788, WO9857996) structural platforms have been identified as inhibitors of p38 kinase or as cytokine inhibitors. Selective inhibitors of p38 kinase are known to suppress the expression of TNF- α and IL-1 β (McKenna, et al., J. Med. Chem., **45**(11), 2173-2184 (2002)). Anti-inflammatory activity for compounds within the pyrimidinylimidazole structural platform has been reported (Lantos, et al., J. Med. Chem., **27**, 72-75 (1984)), and a number of inhibitors of p38 kinase are under active investigation for the treatment of a variety of

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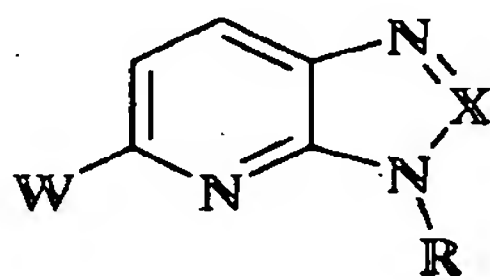
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disorders (Boehm and Adams, Exp. Opin. Ther. Patents, 10(1), 25-37 (2000)). There remains a need for treatment in this field for compounds that are cytokine suppressive drugs, i.e., compounds that are capable of inhibiting p38 kinase.

The present invention provides new inhibitors of p38 kinase useful for the treatment of conditions resulting from excessive cytokine production.

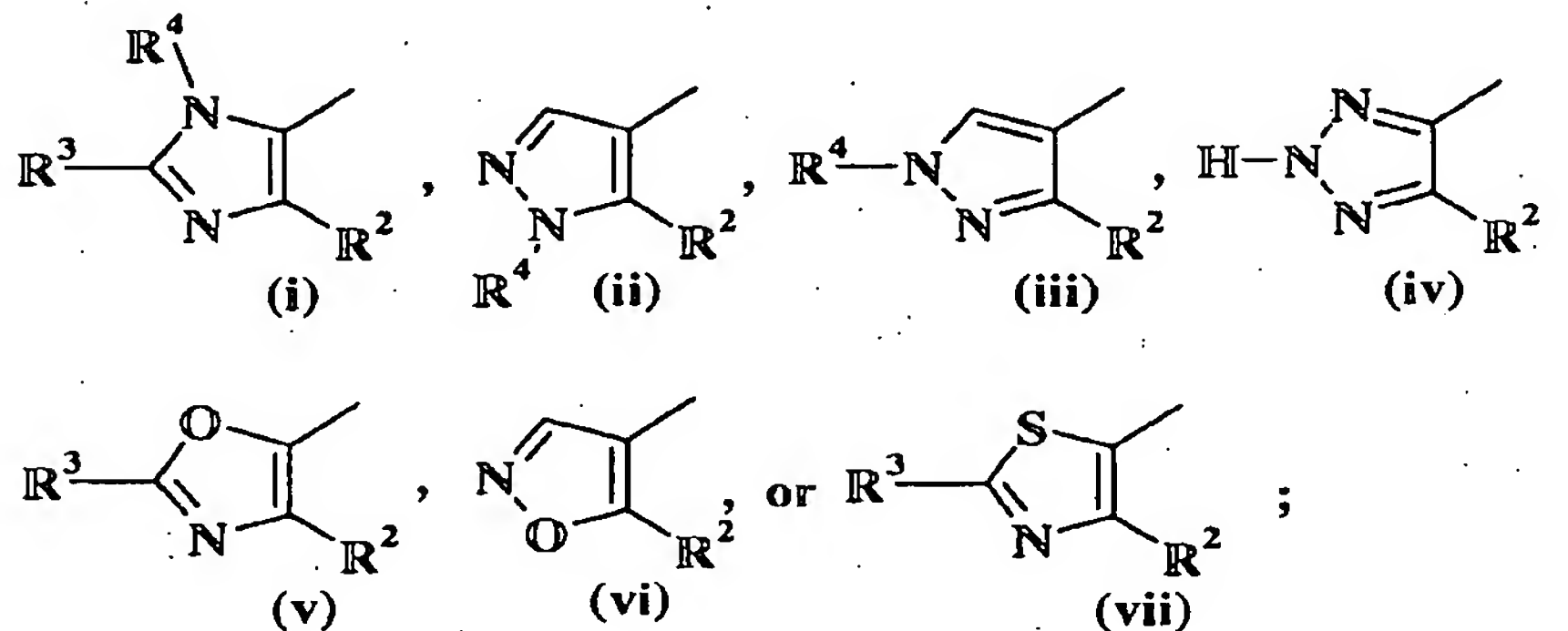
BRIEF SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



I

where:



W is

X is N, or C-R¹;

R is C₁-C₇ alkyl, C₃-C₇ cycloalkyl, (C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl), -SO₂-(C₁-C₇ alkyl), or -SO₂-NR⁵R⁶;

R¹ is hydrogen, amino, methyl, or -N=CH(NMe)₂;

R² is phenyl optionally substituted with one or two substituents independently selected from halo;

R³ is hydrogen, C₁-C₇ alkyl, C₃-C₇ cycloalkyl, or phenyl optionally substituted with one or two substituents independently selected from halo and trifluoromethyl;

R⁴ is hydrogen or C₁-C₇ alkyl;

R^5 and R^6 are independently selected from the group consisting of C_1 - C_7 alkyl; or a pharmaceutically acceptable salt thereof.

The present invention provides a method of inhibiting p-38 kinase in a mammal comprising administering to a mammal in need of such treatment an effective amount of a
5 compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of suppressing the production of tumor necrosis factor α (TNF- α) in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

10 The present invention also provides a method of suppressing the production of interleukin- 1β (IL- 1β) in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of treating conditions resulting
15 from excessive cytokine production in a mammal comprising administering to a mammal in need of such treatment a cytokine-suppressing amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of inhibiting the growth of a susceptible neoplasm in a mammal comprising administering to a mammal in need of
20 such treatment a p38 inhibiting amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of inhibiting metastasis in a mammal comprising administering to a mammal in need of such treatment a p38 inhibiting amount of a compound of Formula I or a pharmaceutically acceptable salt
25 thereof.

The present invention also provides a method of treating rheumatoid arthritis in a mammal comprising administering to a mammal in need of such treatment a p38 inhibiting amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

30 The present invention also provides a pharmaceutical formulation comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

This invention also provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of p38 kinase. Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the inhibition of p38 kinase in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the inhibition of p38 kinase comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof.

This invention also provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the suppression of the production of tumor necrosis factor α (TNF- α). Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the suppression of the production of tumor necrosis factor α (TNF- α) in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the suppression of the production of tumor necrosis factor α (TNF- α) comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the suppression of the production of interleukin-1 β (IL-1 β). Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the suppression of the production of interleukin-1 β (IL-1 β) in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the suppression of the production of interleukin-1 β (IL-1 β) comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of conditions resulting from excessive cytokine production. Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of conditions resulting from excessive cytokine production in mammals. Furthermore, this invention provides a pharmaceutical composition adapted

for the treatment of conditions resulting from excessive cytokine production comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides the use of a compound of Formula I or a
5 pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of growth of a susceptible neoplasm. Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the inhibition of growth of a susceptible neoplasm in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the inhibition of growth of a
10 susceptible neoplasm comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides the use of a compound of Formula I or a
pharmaceutically acceptable salt thereof for the manufacture of a medicament for the
15 inhibition of metastasis. Additionally, this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the inhibition of metastasis in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the inhibition of metastasis comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more
20 pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides the use of a compound of Formula I or a
pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of rheumatoid arthritis. Additionally, this invention provides a compound of
Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of
25 rheumatoid arthritis in mammals. Furthermore, this invention provides a pharmaceutical composition adapted for the treatment of rheumatoid arthritis comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

DETAILED DESCRIPTION OF THE INVENTION

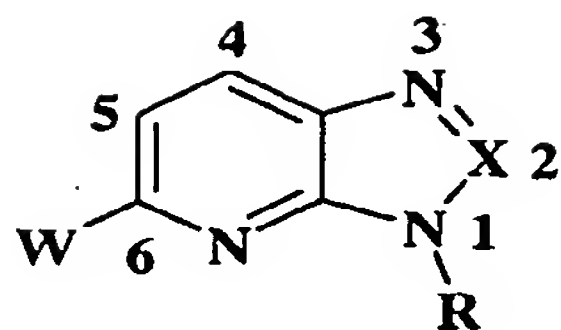
The general chemical terms used in the formulae above have their usual meanings. For example, the term "C₁-C₇ alkyl" includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl and heptyl moieties. The term "C₁-C₇ alkylene" includes methylene, ethylene, propylene, isopropylene, butylene, isobutylene, *sec*-butylene, *tert*-butylene, pentylene, hexylene and heptylene moieties. The term "C₃-C₇ cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl moieties. The term "(C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl)" is taken to mean a C₃-C₇ cycloalkyl attached through a C₁-C₇ alkylene linker. The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "p-38 kinase" is taken to mean the p-38 α and/or p-38 β kinase isoforms.

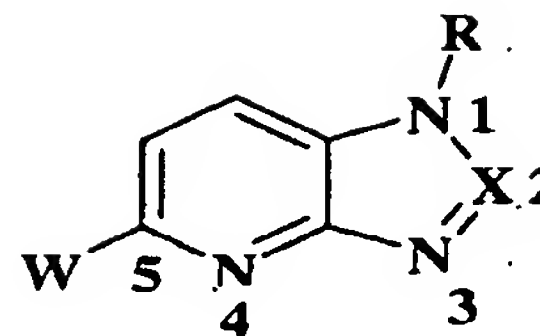
The term "suppressing the production of TNF- α (IL-1 β , cytokine)" is taken to mean decreasing of excessive *in vivo* levels of TNF- α , IL-1 β , or another cytokine in a mammal to normal or sub-normal levels. This may be accomplished by inhibition of the *in vivo* release of TNF- α , IL-1 β , or another cytokine by all cells, including macrophages; by down regulation, at the genomic level, of excessive *in vivo* levels of TNF- α , IL-1 β , or another cytokine in a mammal to normal or sub-normal levels; by inhibition of the synthesis of TNF- α , IL-1 β , or another cytokine as a posttranslational event; or by a down regulation of TNF- α , IL-1 β , or another cytokine at the translational level.

The skilled artisan will appreciate that certain compounds of Formula I contain at least one chiral center. The present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates. It is preferred that compounds of Formula I containing at least one chiral center exist as single enantiomers or diastereomers. The single enantiomers or diastereomers may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomers or diastereomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques.

The skilled artisan will also appreciate that the heteroaryl ring of the pyridinyl-fused heteroaryl moiety in compounds of Formula I exists in tautomeric forms giving rise to regioisomers represented by the following structural formulae:



Tautomer I

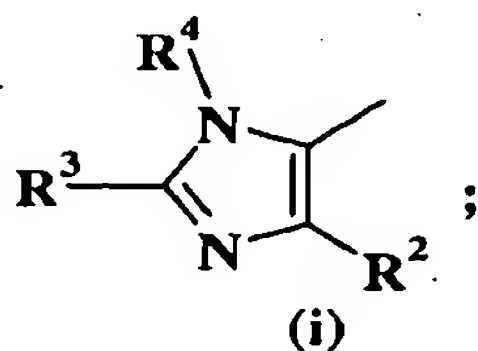


Tautomer II

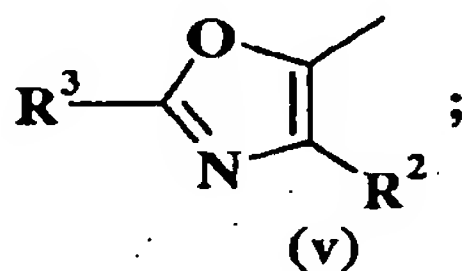
These tautomeric forms give rise to two different numbering conventions. When the compounds of Formula I exist in the form of Tautomer I, the substituent "W" will be attached at the 6-position of the ring. When the compounds of Formula I exist in the form of Tautomer II, the substituent "W" will be attached at the 5-position of the ring. Likewise, the skilled artisan will appreciate that when W is imidazole (i), and R⁴ is hydrogen, the imidazole ring exists in two tautomeric forms. Also when W is triazole (iv), the triazole moiety exists in three tautomeric forms. All of these tautomeric forms and the resulting regioisomers are contemplated by the present invention, and are included in the meaning of the compounds represented by Formula I.

It will be understood by the skilled reader that most or all of the compounds of the present invention are capable of forming salts. In all cases, the pharmaceutically acceptable salts of all of the compounds are included in the names of them. The compounds of the present invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid and methanesulfonic acid.

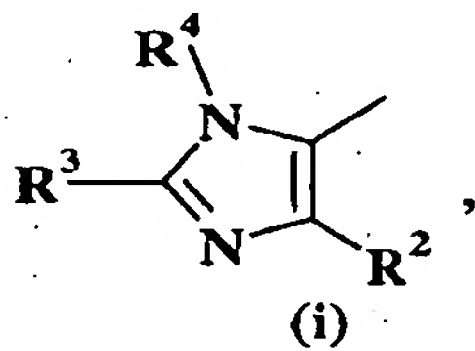
While all of the compounds of Formula I are useful inhibitors of p-38 kinase, certain classes of compounds are preferred. The following paragraphs describe such preferred classes:



a) W is

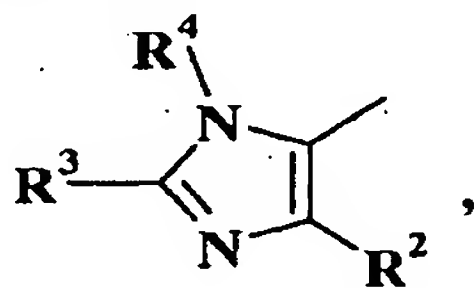


b) W is

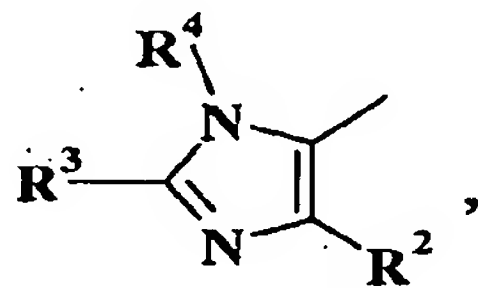
c) X is C-R¹;d) X is C-NH₂;e) R¹ is NH₂;5 f) R² is phenyl, 4-fluorophenyl, or 2,4-difluorophenyl;g) R² is phenyl;h) R² is 4-fluorophenyl;i) R² is 2,4-difluorophenyl;j) R⁴ is hydrogen;

10

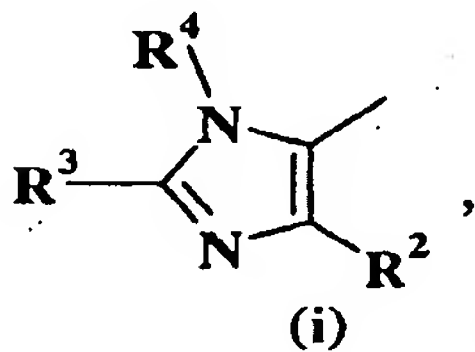
k) W is

X is C-R¹, R² is phenyl, 4-fluorophenyl, or 2,4-difluorophenyl, and R⁴ is hydrogen;

l) W is

X is C-NH₂, R² is phenyl, 4-fluorophenyl, or 2,4-difluorophenyl, and R⁴ is hydrogen;

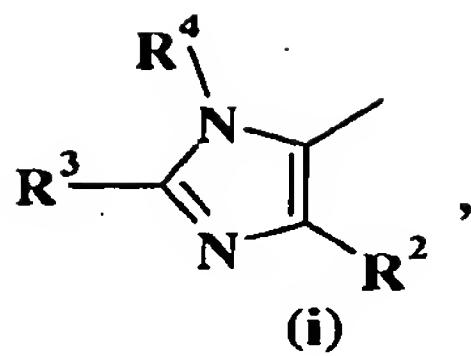
m) W is

X is C-R¹, R² is phenyl, and R⁴ is hydrogen;

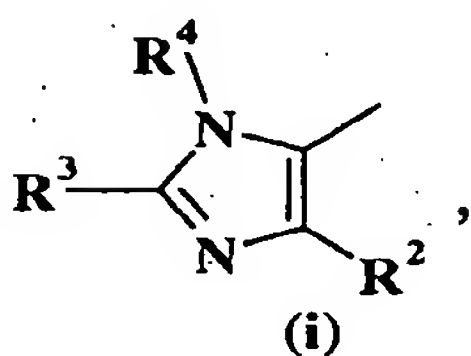
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n) W is

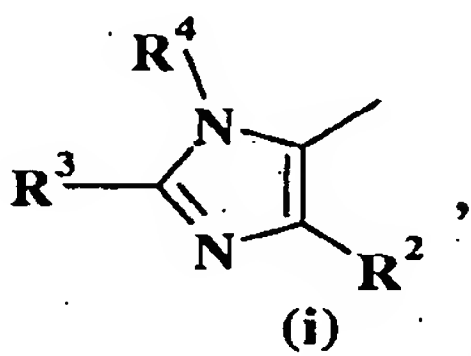
X is C-R¹, R² is 4-fluorophenyl, and R⁴ is hydrogen;



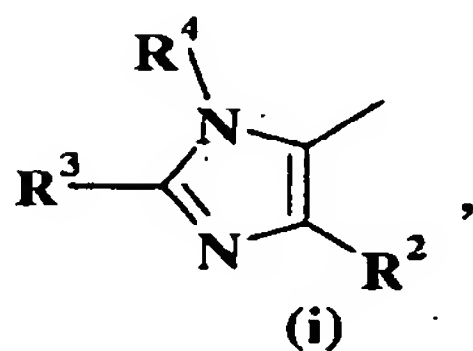
o) W is hydrogen; X is C-R¹, R² is 2,4-difluorophenyl, and R⁴ is



p) W is X is C-NH₂, R² is phenyl, and R⁴ is hydrogen;



q) W is X is C-NH₂, R² is 4-fluorophenyl, and R⁴ is hydrogen;
and



r) W is X is C-NH₂, R² is 2,4-difluorophenyl, and R⁴ is hydrogen.

Preferred embodiments of the present invention include all combinations of paragraphs a) – r).

The compounds of Formula I are inhibitors of p38 kinase. Thus, the present invention also provides a method of inhibiting p38 kinase in a mammal that comprises administering to a mammal in need of said treatment a p38 kinase-inhibiting amount of a compound of Formula I. It is preferred that the mammal to be treated by the administration of the compounds of Formula I is human.

As inhibitors of p38 kinase, the compounds of the present invention are useful for suppressing the production of the pro-inflammatory cytokines tumor necrosis factor α (TNF- α) and interleukin-1 β (IL-1 β), and therefore for the treatment of disorders resulting from excessive cytokine production. The present compounds are therefore believed to be

useful in treating inflammatory disorders, including eczema, atopic dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, and toxic shock syndrome. The compounds of the present invention are also believed to be useful in the treatment of cardiovascular disorders, such as acute myocardial infarction, chronic heart failure, atherosclerosis, viral myocarditis, cardiac allograft rejection, and sepsis-associated cardiac dysfunction. Furthermore, the compounds of the present invention are also believed to be useful for the treatment of central nervous system disorders, such as meningococcal meningitis, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

Most solid tumors increase in mass through the proliferation of malignant cells and stromal cells, including endothelial cells. In order for a tumor to grow larger than 2-3 millimeters in diameter, it must form a vasculature, a process known as angiogenesis. Suppression of tumor-induced angiogenesis by angiostatin and endostatin has been reported to result in antitumor activity (O'Reilly, *et al.*, Cell, **88**, 277-285 (1997)). The selective p38 kinase inhibitor SB22025 has been shown to inhibit angiogenesis (J.R. Jackson, *et al.*, J. Pharmacol. Exp. Therapeutics, **284**, 687 (1998)). Because angiogenesis is a critical component of the mass expansion of most solid tumors, the development of new p38 kinase inhibitors for the inhibition of this process represents a promising approach for antitumor therapy. This approach to antitumor therapy may lack the toxic side effects or drug resistance-inducing properties of conventional chemotherapy (Judah Folkman, Endogenous Inhibitors of Angiogenesis, The Harvey Lectures, Series 92, pages 65-82, Wiley-Liss Inc., (1998)).

As inhibitors of p38 kinase, the compounds of the present invention, therefore, are also useful in inhibiting growth of susceptible neoplasms. Schultz, R. M. *Potential of p38 MAP kinase inhibitors in the treatment of cancer*. In: E. Jucker (ed.), Progress in Drug Research, **60**, 59-92, (2003). A susceptible neoplasm is defined to be a neoplasm that depends upon p38 kinase for its survival, growth, or metastasis. Susceptible neoplasms include tumors of the brain, genitourinary tract, lymphatic system, stomach, larynx, and lung (U.S. Patent #5,717,100). Preferably, the term "susceptible neoplasms" as used in the present application includes human cancers including non-small cell lung carcinoma (A. Greenberg, *et al.*, Am. J. Respir. Cell Mol. Biol., **26**, 558 (2002)), breast carcinoma (J. Chen, *et al.*, J. Biol. Chem., **276**, 47901 (2001); B. Salh, *et al.*, Int. J. Cancer, **98**, 148 (2002); and S. Xiong, *et al.*, Cancer Res., **61**, 1727 (2001)), gastric carcinoma (Y.D. Jung,

et al., Proc. Am. Assoc. Cancer Res., **43**, 9 (2002)), colorectal carcinomas (S. Xiong, et al., Cancer Res., **61**, 1727 (2001)), and malignant melanoma (C. Denkert, et al., Clin. Exp. Metastasis, **19**, 79 (2002)).

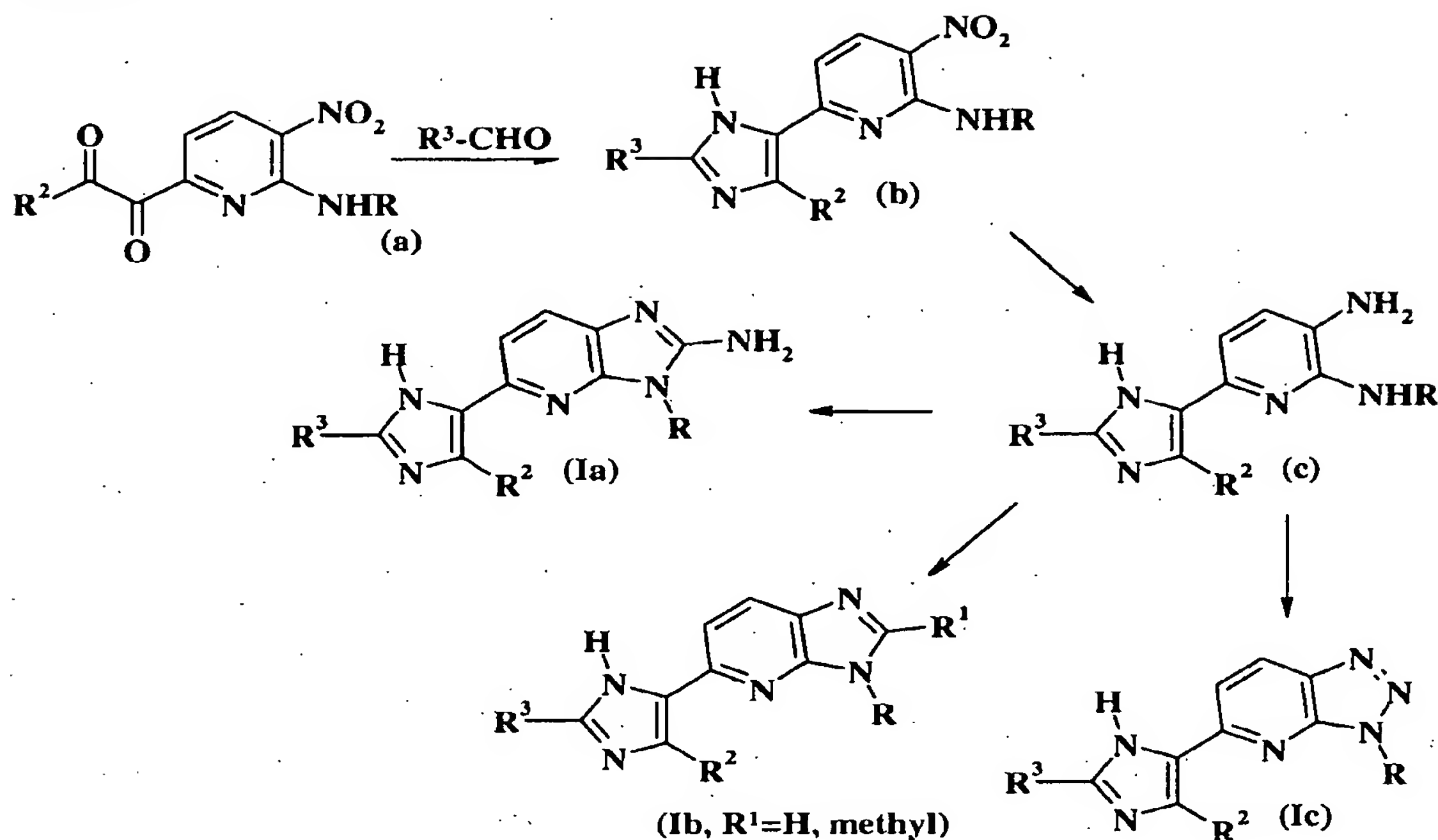
5 Inhibition of angiogenesis by suppression of TNF- α has also been taught to be useful in the inhibition or prevention of metastasis (U.S. Patent #6,414,150; U.S. Patent #6,335,336). Furthermore, suppression of TNF- α is indicated for the treatment and prevention of cachexia, a wasting syndrome experienced by about half of all cancer patients (T. Yoneda, et al., J. Clin. Invest., **87**, 977 (1991)).

10 Furthermore, inhibition of p38 kinase may be effective in the treatment of certain viral conditions such as influenza (K. Kujime, et al., J. Immunology., **164**, 3222-3228 (2000)), rhinovirus (S. Griego, et al., J. Immunology, **165**, 5211-5220 (2000)), and HIV (L. Shapiro, et al., Proc. Natl. Acad. Sci. USA, **95**, 7422-7426, (1998)).

15 The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents have been eliminated in the following schemes for the sake of clarity
20 and are not intended to limit the teaching of the schemes in any way.

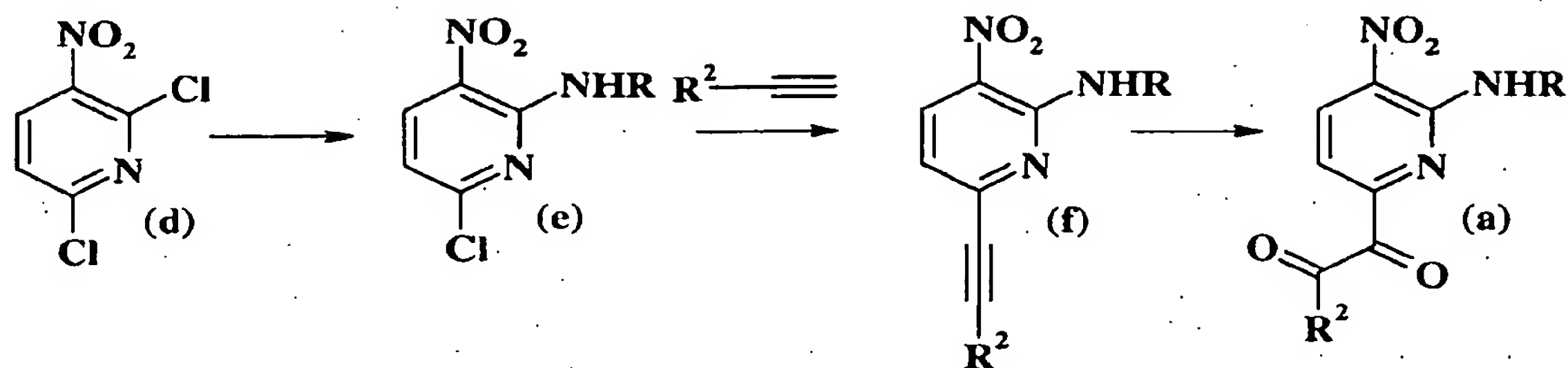
Compounds of Formula I where W is the imidazole (i) may be prepared as illustrated in the following scheme where R, R¹, R², and R³ are as previously defined.

Scheme I



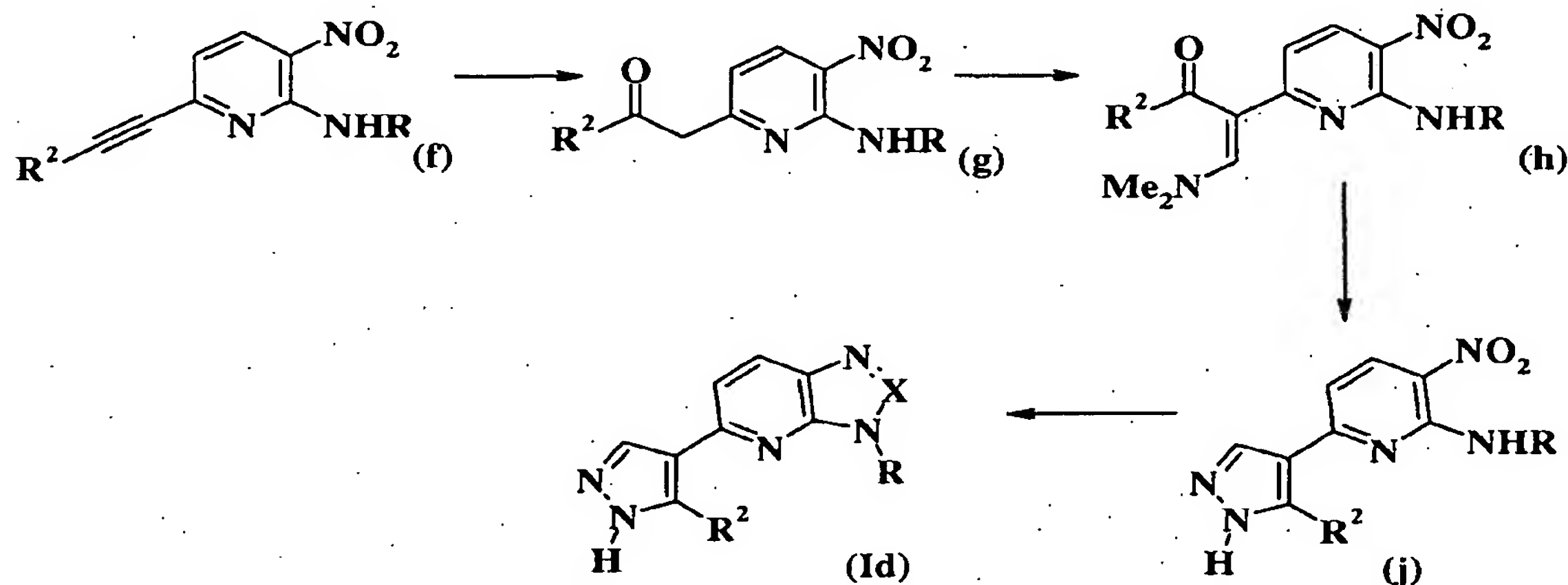
Diketone (a) is reacted with ammonium acetate and an appropriate aldehyde in an appropriate solvent, preferably acetic acid, to provide the corresponding nitropyridinylimidazole (b). The nitro moiety is reduced under standard hydrogenation or chemical conditions to provide the corresponding diamine (c). This diamine is then either reacted with cyanogen bromide to provide the 6-(imidazol-5-yl)-2-aminopyridinylimidazole (Ia), with an appropriate orthoformate to provide the 6-(imidazol-5-yl)pyridinylimidazole (Ib), or with an appropriate nitrite to provide the 6-(imidazol-5-yl)pyridinyltriazole (Ic). The skilled artisan will appreciate that the corresponding 5-(imidazol-5-yl)-pyridinylimidazoles and pyridinyltriazoles may be prepared by beginning with the 3-nitro-4-NHR-diketone isomer of intermediate (a).

The requisite diketones (a) may be prepared as described in the following scheme, where R and R^2 are as previously defined.

Scheme II

5 2,6-dichloronitropyridine (d) and an appropriate amine or amine derivative are heated together in an appropriate solvent to provide the corresponding 2-amino-6-chloro-3-nitropyridine (e), which is then coupled with an appropriately substituted acetylene to provide the corresponding 1,2-disubstituted acetylene (f). This acetylene is oxidized to provide the target diketone (a).

10 Compounds of Formula I where W is pyrazole (ii) or (iii) are prepared as described in the following Scheme where X, R, R¹, and R² are as previously defined.

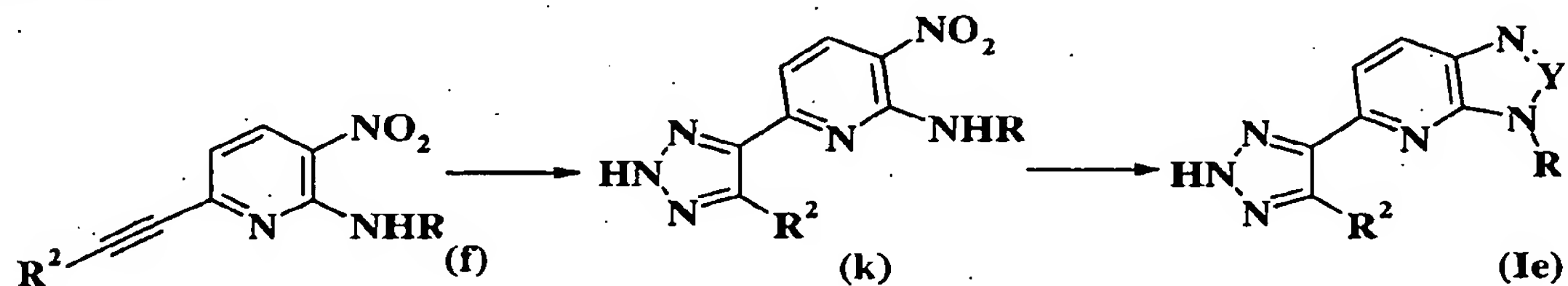
Scheme III

15 Acetylene (f) is treated with mercuric oxide in aqueous sulfuric acid to provide the ketone (g). This ketone is treated with dimethylformamide dimethylacetal or tris(dimethyl-amino)methane in a suitable solvent, typically dimethylformamide, to provide the enaminoketone (h). The enaminoketone is then treated with hydrazine in a suitable solvent, typically ethanol or methanol, to provide the phenylpyrazole (j). The

imidazo- or triazolopyridine moiety is prepared as previously described to provide the compounds of Formula Id.

The compounds of Formula I where W is the [1,2,3]triazole (iv) may be prepared as described in the following Scheme where variables Y, R, and R² are as previously defined.

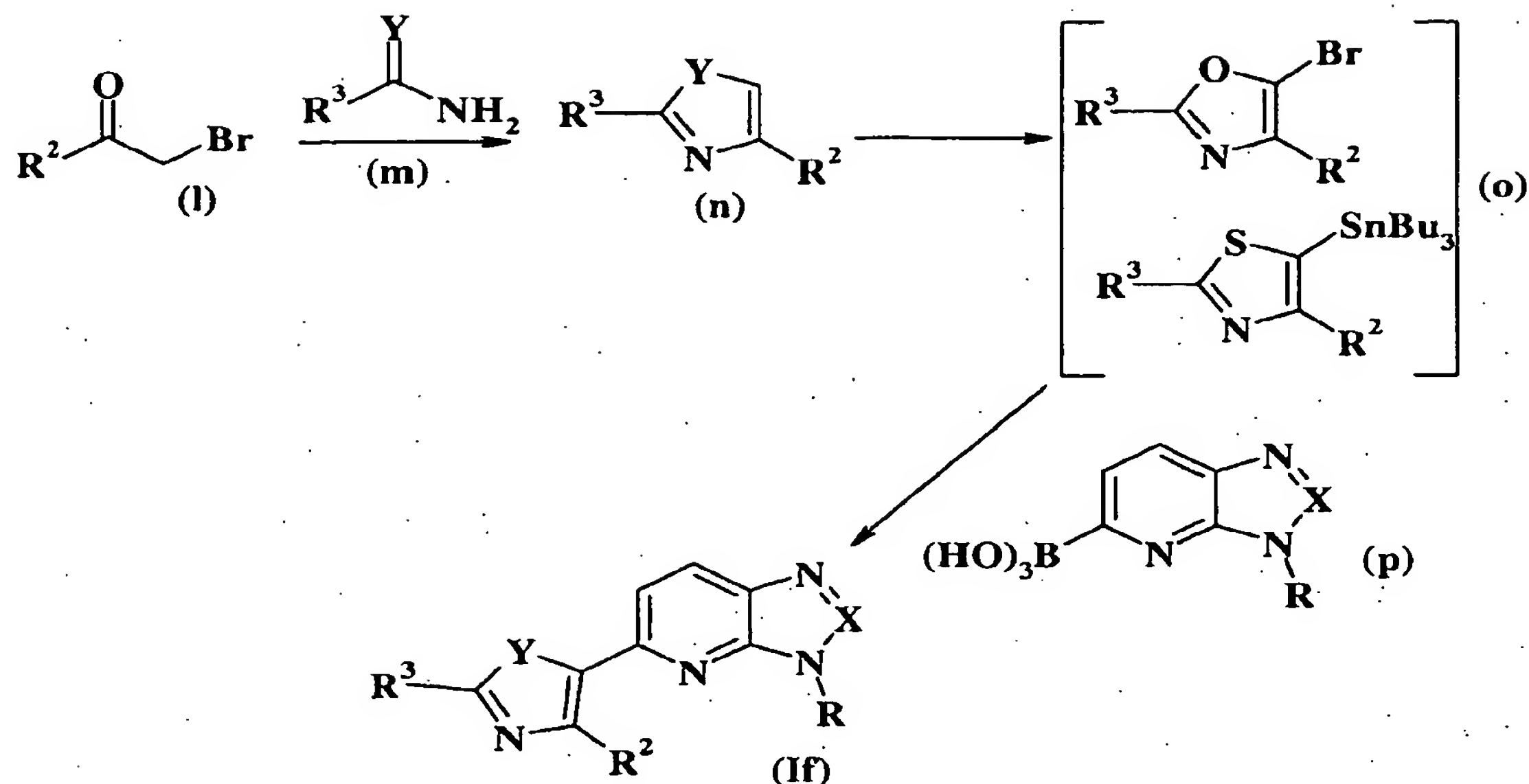
Scheme IV



The acetylene (f) is reacted with a source of azide, typically sodium azide, in a suitable solvent, such as dimethoxyethane to provide the triazole (k). The imidazo- or triazolopyridine moiety is prepared as previously described to provide the compounds of Formula Ie.

The compounds of Formula I where W is the thiazole (v) or oxazole (vii) may be prepared as described in the following Scheme where variables X, R, R², and R³ are as previously defined and Y is O or S.

Scheme V



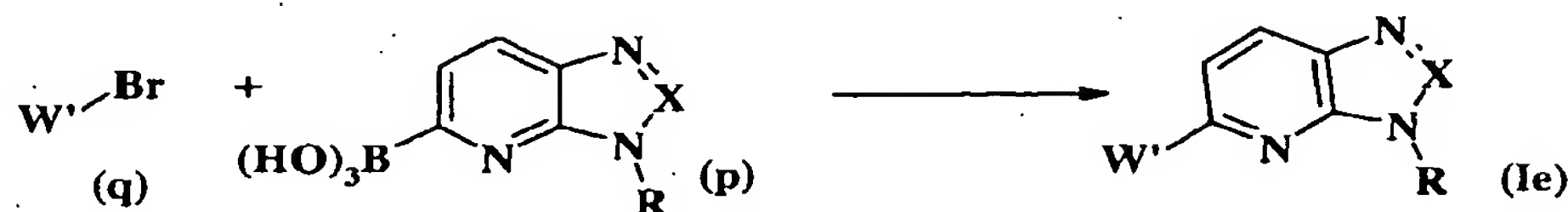
The α -bromoketone (I) is reacted with an appropriate amide (m, Y=O) or thioamide (m, Y=S) in a suitable solvent to provide the corresponding oxazole or thiazole (n). The oxazole (n, Y=O) is then treated with bromine in a suitable solvent to provide the corresponding brominated heterocycle (o, Y=O). The thiazole (n, Y=S) is treated with *n*-butyllithium and the resulting anion reacted with tributyltin chloride to provide the corresponding tin derivative (o, Y=S). The appropriately substituted heterocycle (o) is reacted with an appropriate boronic acid (p) in the presence of a suitable catalyst as previously described to provide the compounds of Formula If.

The requisite α -bromoketones are either commercially available or may be prepared by standard conditions from the corresponding carbonyl compound, for example, as described by House (H.O. House, Modern Synthetic Reactions, W.A. Benjamin, Inc., Menlo Park, California (1972), pages 459-478) and Larock (R.C. Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, New York (1989), pages 369-471, 755). The requisite amides and thioamides are either commercially available or may be prepared by standard methods well known to the skilled artisan.

Additional compounds of Formula I where W is imidazole (i) or isoxazole (vi) may be prepared under standard palladium coupling conditions as described in the

following Scheme, where W' is imidazole (i) or isoxazole (vi), and X and R are as previously defined.

Scheme VI



5 An appropriately substituted haloheteroaryl (q) is coupled with an appropriately substituted boronic acid (p) in the presence of a palladium catalyst, typically bis(triphenylphosphine)palladium(II) chloride, in a suitable solvent to provide the desired compound of Formula Ie. The requisite starting materials are either commercially available or may be prepared by methods well known to one of ordinary skill in the art.

10 Many of the compounds of the present invention are not only inhibitors of p38 kinase, but are also useful intermediates for the preparation of additional compounds of the present invention. For example, primary and secondary amines may be acylated, alkylated or coupled with carboxylic acids or amino acids under standard peptide coupling conditions. Furthermore, ester moieties may be reduced to the corresponding alcohols or
15 converted to amides under standard conditions. Alcohols may be activated and displaced by a number of nucleophiles to provide other compounds of the invention. Such leaving groups include but are not limited to halides, oxonium ions, alkyl perchlorates, ammonioalkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate. Techniques for the introduction of
20 these groups are also well known to the skilled artisan; see, for example, March, Advanced Organic Chemistry, 5th Ed., John Wiley and Sons, New York, pg. 445-449 (2001). Additionally, the 2-amino moiety of the benzimidazole nucleus may be diazotized and displaced to provide additional compounds of the invention under standard conditions.

25 The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the
30 synthesis of the compounds of the present invention. Methods for introducing and

removing nitrogen and oxygen protecting groups are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons, New York, Chapter 7 (1999). Furthermore, the skilled artisan will appreciate that in many circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

The abbreviations, symbols and terms used in the examples and assays have the following meanings.

- 10 AcOH = acetic acid
- Cs₂CO₃ = cesium carbonate
- CH₂Cl₂ = dichloromethane
- DMF = N,N-dimethylformamide
- DMSO = dimethylsulfoxide
- 15 Et₂O = diethyl ether
- EtOAc = ethyl acetate
- EtOH = ethanol
- h = hour(s)
- HCl = hydrochloric acid
- 20 H₂SO₄ = sulfuric acid
- HgO = mercury (II) oxide
- KMnO₄ = potassium permanganate
- MeOH = methanol
- MgSO₄ = magnesium sulfate
- 25 min = minute(s)
- NaCl = sodium chloride
- NaH = sodium hydride
- NaHCO₃ = sodium bicarbonate
- Na₂CO₃ = sodium carbonate
- 30 Na₂SO₃ = sodium sulfite
- Na₂SO₄ = sodium sulfate
- NaOH = sodium hydroxide

NH₄OH = ammonium hydroxide

Pd(OAc)₂ = palladium acetate

RT = room temperature

THF = tetrahydrofuran

5

Preparation 1

[6-(2-tert-Butyl-5-phenyl-3H-imidazol-4-yl)-3-nitropyridin-2-yl]-(2,2-dimethylpropyl)amine

(6-Chloro-3-nitropyridin-2-yl)-(2,2-dimethyl-propyl)amine

10 Add neopentylamine (18 mL, 150 mmol) to a suspension of 2,6-dichloro-3-nitropyridine (20 g, 103 mmol) and Na₂CO₃ (18.5 g, 175 mmol) in EtOH 1 (1.6 mL/mmol) at RT and stir overnight. Concentrate and dilute the resultant slurry with water (100 mL) and slowly neutralize with concentrated HCl (approx. 40 mL) to pH = 7. Cool the suspension at 0 °C for 1 h and collect solid by vacuum filtration. Wash the solid with
15 ice water (4 x 50 mL) and air dry overnight. Recrystallize the material from EtOAc and hexanes to give the title compound as a yellow solid (21.23 g, 84%).

MS (ES): $m/z = 244$ [M+H]

(2,2-Dimethylpropyl)-(3-nitro-6-phenylethynylpyridin-2-yl)amine

20 Dissolve (6-chloro-3-nitropyridin-2-yl)-(2,2-dimethylpropyl)amine (7.3 g, 30.0 mmol), phenylacetylene (5.0 mL, 45 mmol) and triphenylphosphine (1.5 mmol, 0.39 g) in triethylamine (10 mL/g) in an oven-dried round bottom flask is flushed with nitrogen and evacuated three times. Add Pd(OAc)₂ (0.10 g, 0.45 mmol) and the nitrogen flush/evacuation cycle is repeated (3x). Heat at 70-80 °C with stirring under nitrogen for
25 1-3 h, then cool at RT for 2 h. Concentrate and partition between water (25 mL) and EtOAc (150 mL). Separate the organic layer and wash with water (4 x 25 mL), saturated aqueous NaCl (25 mL), dry with MgSO₄, filter, and concentrate. Purify the crude solid by recrystallization from EtOAc /hexanes to give the title product as a bright orange solid (6.5 g, 21.2 mmol, 71%).

30 MS (ES): $m/z = 310$ [M+H]; mp 90-92 °C.

1-[6-(2,2-Dimethylpropylamino)-5-nitropyridin-2-yl]-2-phenylethane-1,2-dione

Cool a mixture of (2,2-dimethylpropyl)-(3-nitro-6-phenylethynylpyridin-2-yl)amine (3.11 g, 10 mmol), NaHCO₃ (0.420 g, 5.0 mmol), MgSO₄ (2.40 g, 20 mmol) in acetone (85 mL), and water (25 mL) and cool to 0 °C. Add KMnO₄ (3.16 g, 20.0 mmol) to the cooled mixture, and stir the reaction mixture vigorously at 0 °C for about 1-2 h.

- 5 Quench the mixture with Na₂SO₃ (5.67 g, 45 mmol). Remove ice bath and stir mixture at RT for 2 h. Filter the solid through a pad of filtering agent. Wash with water (2 x 50 mL) and EtOAc (50 mL). Separate the phases and extract the aqueous phase with EtOAc (3 x 50 mL). Wash the combined organic phases with saturated aqueous NaCl (25 mL), dry with MgSO₄, filter and concentrate. Purify the crude (silica gel chromatography, eluting with 1:1 hexanes:CH₂Cl₂) to give the title compound (1.586 g, 46%).
- 10

MS (ES): m/z = 342 [M+H]; mp 88-90 °C.

[6-(2-tert-Butyl-5-phenyl-3H-imidazol-4-yl)-3-nitropyridin-2-yl]-(2,2-dimethylpropyl)amine

- 15 Heat a mixture of 1-[6-(2,2-dimethylpropylamino)-5-nitropyridin-2-yl]-2-phenylethane-1,2-dione (1.0241 g, 3.0 mmol), trimethylacetaldehyde (0.66 mL, 6.0 mmol), ammonium acetate (3.47 g, 45 mmol) in AcOH (5 mL/mmol) at 80 °C with monitoring by liquid chromatography—mass spectroscopy for the appearance of product. Cool the reaction mixture to 0 °C and neutralize to pH 7 with 5.0 N NaOH. Extract the
- 20 neutralized aqueous phase with EtOAc (3 x 20 mL) and wash the combined organic phases with 20 mL portions of saturated aqueous NaHCO₃ until no further neutralization is observed. Dry the organic phase with MgSO₄, filter, and concentrate. Triturate the orange crude solid with EtOAc to obtain the title compound (0.7578 g, 62%).

MS (ES): m/z = 408 [M+H]; mp 224-226 °C.

25

The compounds of Preparations 2-21 may be prepared essentially as described in Preparation 1.

| Prep. | Compound | MS (ES): <i>m/z</i> [M+H] |
|-------|--|------------------------------|
| 2 | {6-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 464 |
| 3 | {6-[2-(2,6-Dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 496 |
| 4 | {6-[2-(2-Chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 480 |
| 5 | (2,2-Dimethylpropyl){6-[5-(4-fluorophenyl)-2-isopropyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 412 |
| 6 | Cyclopropylmethyl{6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 448 |
| 7 | Cyclopropylmethyl{6-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 480 |
| 8 | Cyclopropylmethyl{6-[2-(2,6-difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 466 |
| 9 | Cyclopropylmethyl{6-[2-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 498 |
| 10 | Cyclopropylmethyl{6-[5-(4-fluorophenyl)-2-isopropyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 396 |
| 11 | [6-(2- <u>tert</u> -Butyl-5-phenyl-3H-imidazol-4-yl)-3-nitropyridin-2-yl]cyclopropylmethylamine | 392 |
| 12 | {6-[2-(2,6-Difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 482 |
| 13 | {6-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}cyclopropylmethylamine | 426 |
| 14 | [6-(2-Cyclopropyl-5-phenyl-3H-imidazol-4-yl)-3-nitropyridin-2-yl]-(2,2-dimethylpropyl)amine | 392 |
| 15 | (2,2-Dimethylpropyl)-{6-[5-(4-fluorophenyl)-2-(2-fluoro-6-trifluoromethylphenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 532 |
| 16 | (2,2-Dimethylpropyl)-{6-[2-(2-fluoro-6-trifluoromethylphenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine | 514 |
| 17 | {6-[2-Cyclopropyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 410 |
| 18 | {6-[2-(2,6-Dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 514 |
| 19 | {6-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 410 |
| 20 | {6-[2- <u>tert</u> -Butyl-5-(2,4-difluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 444 |
| 21 | {6-[5-(2,4-Difluorophenyl)-2-(2,6-difluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine | 500 |

Preparation 22

6-[2-(2,6-Dichlorophenyl)-5-phenyl-1H-imidazol-4-yl]-N²-isobutylpyridine-2,3-diamine

Add sodium dithionite (2.58 g, 14.82 mmol) followed by 32% NH₄OH (9 mL) to a solution of {6-[2-(2,6-dichlorophenyl)-5-phenyl-1H-imidazol-4-yl]-3-nitropyridin-2-yl}isobutylamine (1.43 g, 2.96 mmol) in 50 mL of 1:1 THF:water mixture. Stir the mixture at RT for 2 h. Dilute with EtOAc. Wash the organic layer with saturated aqueous NaCl and dry the organic phase over Na₂SO₄. Concentrate to yield the title compound (1.32 g, 98%).

Preparation 23

2-Isobutylamino-3-nitro-6-[3-(4-fluorophenyl)-1-morpholinoethylpyrazol-4-yl]pyridine

2-Isobutylamino-3-nitro-6-(4-fluorophenylethanone)pyridine

Add an aqueous suspension of HgO (0.55 g, 2.54 mmol) in 100 mL of 4% H₂SO₄ to a solution of 2-isobutylamino-3-nitro-6-(4-fluorophenyl)ethynylpyridine (3.99 g, 12.7 mmol) in 100 mL of MeOH. Stir at 95 °C for 17 h and cool to RT. Filter the mixture through a filtering agent and dissolve the precipitate with EtOAc (5 x 100 mL).

Concentrate and wash the residue with 10:2:1 hexane:diethyl ether:MeOH (130 mL) to provide the title compound (2.60 g, 62%).

MS (ES): m/z = 332 [M+H].

2-Isobutylamino-3-nitro-6-[3-(4-fluorophenyl)pyrazol-4-yl]pyridine.

Add dimethylformamide dimethyl acetal (4.50 mL, 33.8 mmol) to a stirred solution of 2-isobutylamino-3-nitro-6-(4-fluorophenyl-ethanone)-pyridine (5.63 g, 16.1 mmol) in 15 mL of dry DMF. Heat the mixture at 80 °C for 6 h, cool to RT and concentrate. Dissolve the residue in 100 mL of EtOH, add 8.30 mL of hydrazine (80% in H₂O), stir for 2 h and concentrate. Purify the residue (silica gel chromatography, eluting with hexanes:EtOAc 1:1) to give the title compound (4.51 g, 75%).

MS (ES): m/z = 356 [M+H].

2-Isobutylamino-3-nitro-6-[3-(4-fluorophenyl)-1-morpholinoethylpyrazol-4-yl]pyridine

Treat a solution of 2-isobutylamino-3-nitro-6-[3-(4-fluorophenyl)pyrazol-4-yl]pyridine (1.25 g, 3.52 mmol) in dry DMF (15 mL) with 95% NaH (0.36 g, 14.3 mmol) at 0 °C for 15 min. Add morpholinoethylchloride hydrochloride (0.983 g, 5.28 mmol) and slowly warm to RT. Add additional NaH (0.36 g, 14.3 mmol), after 1 h and stir the reaction mixture for 24 h. Quench with MeOH (1 mL) and dilute with water (30 mL). Extract with EtOAc (100 mL), dry with MgSO₄, and concentrate. Purify the residue (silica gel chromatography, eluting with hexanes:EtOAc 1:2) to give the title compound (1.35 g, 81%).

MS (ES): $m/z = 469$ [M+H].

Preparation 24

(2,2-Dimethylpropyl)-[3-nitro-6-(5-phenyl-3H-[1,2,3]triazol-4-yl)-pyridin-2-yl]amine

Add sodium azide (0.065 g) to a solution of 2,2-dimethylpropyl-(2-nitro-5-phenylethynylphenyl)amine (0.153 g) in of DMSO (2.5 mL). Heat at 80 °C for 2 h. Cool to RT. Add 10 mL of 1N HCl and extract with EtOAc (20 mL) and wash with saturated aqueous NaCl (2 x 10 mL). Dry the remaining organic phase over Na₂SO₄ and concentrate. Purify the residue (silica gel chromatography, eluting with EtOAc:hexanes 1:2) to give the title compound as yellow solid (0.176 g, 100%).

MS (ES): $m/z = 353$ [M+H].

Preparation 25

2-Amino-5-(2-oxo-2-phenylacetyl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide
N,N-dimethyl-N'-(6-chloro-3-nitropyridin-2-yl)sulfonic acid

Stir a mixture of 2,6-dichloro-3-nitropyridine (1 g, 2.60 mmol) and N,N-dimethylsulfamide (0.78 g, 3.12 mmol) in dry DMF (5 mL). Add lithium hydride (0.11 g, 6.76 mmol) and stir at RT overnight. Add 10 mL of water and 3N HCl until pH = 7. Filter the yellow solid to provide the title compound (85%).

MS (ES): $m/z = 279$ [M+H].

N,N-dimethyl-N'-(3-nitro-6-phenylethynylpyridin-2-yl)sulfonic acid

- Bubble nitrogen through a mixture of N,N-dimethyl-N'-(6-chloro-3-nitropyridin-2-yl)sulfonic acid (3.86 g, 13.7 mmol), phenylacetylene (2.3 mL, 20.67 mmol), triphenylphosphine (0.09 g, 0.68 mmol) and copper (I) iodide (0.06 g, 0.34 mmol) in triethylamine (30 mL) and THF (60 mL) for 3 min. Add bis(triphenylphosphine)palladium (II) chloride (0.24 g, 0.34 mmol) to the mixture and heat at 110 °C for 4 h. Filter through a pad of filtering agent and concentrate. Purify the residue (silica gel chromatography, eluting with 1:1 hexanes:EtOAc) to give the title compound (80%).
- MS (ES): $m/z = 346$ [M+H].

N,N-dimethyl-N'-(3-amino-6-phenylethynylpyridin-2-yl)sulfonic acid

- Stir a mixture of N,N-dimethyl-N'-(3-nitro-6-phenylethynylpyridin-2-yl)sulfonic acid (0.09 g, 0.26 mmol) and tin chloride dihydrate (0.35 g, 1.56 mmol) in EtOAc (5 mL) and EtOH (2.5 mL) at 70 °C for 2 h. Concentrate and purify the residue (silica gel chromatography, eluting with 1:1 hexanes:EtOAc) to give the title compound (65%).
- MS (ES): $m/z = 317$ [M+H].

2-Amino-5-phenylethynylimidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide

- Stir a mixture of N,N-dimethyl-N'-(3-amino-6-phenylethynylpyridin-2-yl)sulfonic acid (0.20 g, 0.63 mmol), cyanogen bromide (0.07 g, 0.69 mmol) and lithium methoxide (0.04 g, 0.94 mmol) in 1,2 dichloroethane (20 mL) at 80 °C overnight. Concentrate and purify the residue (silica gel chromatography, eluting with 1:1 hexanes:EtOAc) to give the title compound (45%).
- MS (ES): $m/z = 342$ [M+H].

2-Amino-5-(2-oxo-2-phenylacetyl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide

- Add a solution of 2-amino-5-phenylethynylimidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide (0.10 g, 0.31 mmol) in acetone (4 mL) over a mechanically stirred solution of NaHCO₃ (0.01 g, 0.15 mmol) and MgSO₄ (0.07 g, 0.62 mmol) in water (4 mL) at 0 °C. Add KMnO₄ (0.12 g, 0.748 mmol) and stir at 0 °C overnight. Add Na₂SO₃ (0.13 g), and stir for 1 h. Add EtOAc and wash with a saturated aqueous solution of NaCl, and

concentrate to give the title compound as an orange solid which is used without further purification (68% yield).

MS (ES): $m/z = 372$ [M+H].

5

Preparation 26

Propane-2-sulfonic acid {3-amino-6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]pyridin-2-yl}amide

Propane-2-sulfonic acid (3-nitro-6-phenylethynylpyridin-2-yl)amide

10 Add propane-2-sulfonic acid (5-chloro-2-nitrophenyl)amide (10 g, 35.7mmol), phenylacetylene (5.9 mL, 53.6mmol) and triphenylphosphine (0.46 g, 1.78 mmol) to a solution of triethylamine (25 mL, 178.5mmol) in dry THF (25 mL) and flush the system with nitrogen. Add dichlorobis(triphenylphosphine)palladium(II) (0.625 g, 0.89 mmol) and copper (I) iodide (0.17 g, 0.89mmol) to this stirring mixture. Heat the reaction to reflux for 4 h. Cool to RT and concentrate to a slurry. Filter the crude material through a
15 plug of silica gel using EtOAc as the eluting solvent. Concentrate the filtrate and crystallize the title compound from EtOAc-hexanes (7.9 g, 64%).

MS (ES): $m/z = 346$ [M+H].

Propane-2-sulfonic acid [3-nitro-6-(2-oxo-2-phenylacetyl)pyridin-2-yl]amide

20 Heat a mixture of propane-2-sulfonic acid (3-nitro-6-phenylethynylpyridin-2-yl)amide (1.8 g, 5.26 mmol) and palladium (II) chloride (0.93 g, 0.53mmol) in dry DMSO (20 mL) at 120 °C for 12 h under a nitrogen atmosphere. Cool to RT, concentrate to a slurry, and purify (silica gel chromatography, eluting with a gradient of 20:80 EtOAc:hexanes to 30:70 EtOAc:hexanes) to give the title compound (1.07 g, 54%).
25 MS (ES): $m/z = 346$ [M+H].

Propane-2-sulfonic acid {6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amide

30 Heat a mixture of propane-2-sulfonic acid [3-nitro-6-(2-oxo-2-phenylacetyl)pyridin-2-yl]amide(0.25g, 0.67mmol), 2,6-difluorobenzaldehyde (0.146 mL, 1.35mmol) and ammonium acetate (0.78 g, 10.05 mmol) in AcOH (5 mL) at 110 °C for

2 h. Cool to RT and concentrate. Dilute with EtOAc (30 mL), extract successively with saturated NaHCO₃ and saturated aqueous NaCl. Dry the organic layer over NaSO₄, concentrate, and purify (silica gel chromatography, eluting with 30:70 EtOAc:hexanes) to give the title compound (0.32 g, 95%).

5 MS (ES): m/z = 500 [M+H].

Propane-2-sulfonic acid {3-amino-6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-pyridin-2-yl}amide

10 Add 10% Pd/C (0.033 g) to a stirring solution of propane-2-sulfonic acid {6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amide (0.33g, 0.66 mmol) in MeOH (10 mL). Add sodium borohydride (0.124 g, 3.3 mmol) in portions and with stirring under nitrogen for 15 min. Filter the catalyst and concentrate. Dilute with EtOAc (20 mL) and extract successively with saturated NaHCO₃ and saturated aqueous NaCl. Dry the organic layer over Na₂SO₄ and concentrate to give the title compound (0.3
15 g, 98%).

MS (ES): m/z = 470 [M+H].

Preparation 27

20 Propane-2-sulfonic acid {3-amino-6-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-pyridin-2-yl}amide

Heat a mixture of propane-2-sulfonic acid {6-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amide (0.262 g, 0.49 mmol) and tin (II) chloride dihydrate (0.55 g, 2.46 mmol) in EtOH (10 mL) at 100 °C for 1 h. Cool to RT and concentrate to a slurry. Pour the reaction mixture into saturated NaHCO₃ (20 mL) and
25 add a filtering agent. Filter and wash with EtOAc. Separate the layers and extract successively with saturated NaHCO₃ and saturated aqueous NaCl. Dry the organic layer over Na₂SO₄ and concentrate to give the title compound (0.21g, 85%).

MS (ES): m/z = 504 [M+H].

Preparation 28

1-Benzyl-2-methyl-4-bromo-5-(2,4-difluorophenyl)-1H-imidazole

1-Benzyl-2-methyl-5-bromo-1H-imidazole

Add N-bromosuccinimide (7.85 g, 44 mmol) to a solution of 1-benzyl-2-methyl-1H-imidazole (8.0 g, 46 mmol) in chloroform (200 mL) and stir for 6 h. Wash with saturated aqueous sodium hydrogen carbonate and saturated aqueous NaCl, dry over MgSO₄, and filter through a pad of silica gel. Concentrate filtrate and suspend the residue in diethyl ether (600 mL), heat to reflux, and filter hot. Concentrate ether filtrate to give the title compound as a tan solid (9.3 g) of the desired compound as a tan solid.

MS (ES): $m/z = 252$ [M+H].

1-Benzyl-2-methyl-5-(2,4-difluorophenyl)-1H-imidazole

Heat a mixture of 1-benzyl-2-methyl-5-bromo-1H-imidazole (4.71 g, 18.7 mmol), 2,4-difluorophenyl boronic acid (6.92 g, 43.8 mmol), bis(acetato)bis(triphenylphosphine)palladium(II) (1.4 g, 1.875 mmol), 2N Na₂CO₃ (19 mL, 38 mmol), MeOH (19 mL) and 1,2-dimethoxyethane (120 mL) to reflux for 18 h. Cool to RT. Add water and EtOAc and separate the layers. Dry organic layer over MgSO₄, filter, and concentrate. Purify the residue (silica gel chromatography, eluting with EtOAc:CH₂Cl₂ mixtures) to give the title compound (3.59 g).

MS (ES): $m/z = 285$ [M+H].

Bromination

Stir a mixture of 1-benzyl-2-methyl-5-(2,4-difluorophenyl)-1H-imidazole (3.58 g, 12.6 mmol), N-bromosuccinimide (2.24 g, 12.6 mmol), and chloroform (100 mL) at RT for 18 h. Add the reaction mixture directly onto silica gel and elute with CH₂Cl₂:EtOAc mixtures to give title compound (3.41 g).

MS (ES): $m/z = 364$ [M+H].

Preparation 29

2-tert-Butyl-4-(4-fluorophenyl)oxazole

Reflux a solution of commercially available 2-bromo-4'-fluoroacetophenone (100.00 g, 460 mmol), 2,2-dimethyl-propionamide (93.06 g, 20 mmol) in 1,4-dioxane

(600 mL) for 2 days. Filter precipitate, concentrate filtrate, and purify (silica gel chromatography, eluting with hexanes:EtOAc 60:1) to give the title compound (55 g, 55%).

MS (ES): m/z = 220 [M+H].

5

The compounds of Preparation 30-31 may be prepared essentially as described in Preparation 29.

| Prep. | Compound | MS (ES): m/z [M+H] |
|-------|---|-------------------------|
| 30 | 2- <u>tert</u> -Butyl-4-(2,4-difluorophenyl)oxazole | 238 |
| 31 | 4-(4-Fluorophenyl)-2-isopropyloxazole | 206 |

Preparation 32

10

2-tert-Butyl-4-(4-fluorophenyl)-5-trimethylstannanyloxazole

Dissolve 2-tert-butyl-4-(4-fluorophenyl)oxazole (0.61 g, 2.77 mmol) in THF (15 ml) and add tert-butyl lithium (3.3 ml, 1.7 M) at -78°C . Stir the mixture for 45 min. Add trimethylstannanyl chloride (0.58 g, 2.90 mmol) and allow the temperature to reach RT. Stir for 2 h and add an ammonium chloride solution (200 μmL , pH = 8 with ammonia) and concentrate.

15

^1H NMR (CDCl_3) δ 7.46 (m, 2H), 6.95 (m, 2H), 1.32 (s, 9H), 0.24 (s, 9H).

Preparation 33

4-(4-Fluorophenyl)-2-methylthiazole

20

Reflux a solution of 2-bromo-4'-fluoroacetophenone (10 g, 46 mmol) and thioacetamide (6.9 g, 92 mmol) in 1,4-dioxane (60 mL) for 3h. Filter the precipitate and wash with EtOAc to give the title compound (6.5 g, 73%).

MS (ES): m/z = 194 [M+H].

25

The compound of Preparation 34 may be prepared essentially as described in Preparation 33.

| Prep. | Compound | MS (ES): m/z [M+H] |
|-------|---------------------------|-------------------------|
| 34 | 2-Methyl-4-phenylthiazole | 176 |

Preparation 35

2-Amino-5-bromoimidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide

2,6-Dibromo-3-nitropyridine

- 5 Heat at 50 °C a mixture of 2,6-dichloro-3-nitropyridine (9 g) and hydrobromic acid (90 mL) in AcOH (30%) overnight. Cool to RT and pour into water (600 mL). Filter the solid to provide the title compound (87%).

¹H NMR (CDCl₃) δ 7.93(d, J= 8.14 Hz, 1H), 7.55 (d, J= 8.14 Hz, 1H).

10. N,N-Dimethyl-N'-(6-bromo-3-nitropyridin-2-yl)sulfonic acid

Stir a mixture of 2,6-dibromo-3-nitropyridine (11.3g, 39.25 mmol) and N, N-dimethylsulfamide (0.006 g, 47.10 mmol) in DMF (40 mL). Add lithium hydride (0.81 g, 102.05 mmol) and stir at RT overnight. Add 100 mL of water and 3 N HCl until pH = 7. Filter the yellow solid to provide the title compound (93%).

- 15 ¹H NMR (DMSO-d₆) δ 10.25 (br s, 1H), 8.41(d, J= 8.59 Hz, 1H), 7.50 (d, J= 8.59 Hz, 1H), 2.95 (2, 6H).

N,N-dimethyl-N'-(3-amino-6-bromo-pyridin-2-yl)-sulfonic acid

- 20 Heat a mixture of N,N-dimethyl-N'-(6-bromo-3-nitropyridin-2-yl)sulfonic acid (11.6 g, 35.69 mmol) and tin chloride (40 g, 178 mmol) in EtOAc:EtOH 500:250 mL for 4 h. Concentrate and purify the residue (silica gel chromatography, eluting with 1:1 hexane:EtOAc). Triturate with water to provide the title compound (85%).

MS (ES): *m/z* = 297 [M+H].

25

2-Amino-5-bromoimidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide

- 30 Stir a mixture of N,N-dimethyl-N'-(3-amino-6-bromopyridin-2-yl)sulfonic acid (0.40 g, 1.35 mmol), cyanogen bromide (0.08 g, 1.48 mmol) and lithium methoxide (0.08 g, 2.02 mmol) in 1,2 dichloroethane (400 mL). Stir at 80 °C for 2 h. Concentrate and purify the residue (silica gel chromatography, eluting with 1:1 hexane:EtOAc) to give the title compound (82%).

MS (ES): *m/z* = 322 [M+H].

EXAMPLE 1

5-(2-tert-Butyl-5-phenyl-3H-imidazol-4-yl)-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate

- 5 Stir a suspension of 6-(2-tert-butyl-5-phenyl-3H-imidazol-4-yl)-3-nitropyridin-2-yl]-(2,2-dimethylpropyl)amine (0.20 g, 0.5 mmol) and 10% palladium on carbon (0.025 g) in EtOH (10 mL) under a balloon of hydrogen overnight. Filter the suspension through a filtering agent and wash with EtOH (2 x 5 mL). Concentrate the filtrate to about 5 mL, and treat at RT with cyanogen bromide (1.3 mmol). Quench with saturated aqueous
- 10 sodium bicarbonate (2 mL) and stir for 15 – 60 min. Dilute the mixture with water (5 mL) and extract with CH₂Cl₂ (2 x 10 mL). Wash the combined organic phases with saturated aqueous NaCl (5 mL), dry with MgSO₄, filter, concentrate, and purify (silica gel chromatography, eluting with a step gradient beginning with 100% CH₂Cl₂, to 5:95 ammoniated MeOH:CH₂Cl₂) to give the desired compound. The free base is isolated and
- 15 then converted to the methanesulfonate salt by treatment of a MeOH-water solution with methanesulfonic acid followed by lyophilization to give the title compound.
- MS (ES): m/z = 402 [M+H].

- The compounds of EXAMPLES 2-14 may be prepared essentially as described in
- 20 EXAMPLE 1.

| EXAMPLE | Compound | MS (ES): m/z [M+H] |
|---------|---|-------------------------|
| 2 | 5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 459 |
| 3 | 5-(2- <u>tert</u> -Butyl-5-phenyl-3H-imidazol-4-yl)-3-cyclopropylmethyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 387 |
| 4 | 5-(2-Cyclopropyl-5-phenyl-3H-imidazol-4-yl)-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 387 |
| 5 | 3-(2,2-Dimethylpropyl)-5-[5-(4-fluorophenyl)-2-(2-fluoro-6-trifluoromethylphenyl)-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 527 |
| 6 | 3-(2,2-Dimethylpropyl)-5-[2-(2-fluoro-6-trifluoromethylphenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 509 |

| | | |
|----|--|-----|
| 7 | 5-[2-Cyclopropyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 405 |
| 8 | 5-[2-(2,6-Difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 477 |
| 9 | 5-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 421 |
| 10 | 5-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-cyclopropylmethyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 405 |
| 11 | 5-[2- <u>tert</u> -Butyl-5-(2,4-difluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 439 |
| 12 | R-5-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(1,2,2-trimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 435 |
| 13 | R-5-[2-(2,6-Difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(1,2,2-trimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 491 |
| 14 | R-5-[5-(4-Fluorophenyl)-2-(2-fluoro-6-trifluoromethylphenyl)-3H-imidazol-4-yl]-3-(1,2,2-trimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 541 |

EXAMPLE 15

3-Cyclopropylmethyl-5-[2-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-
 3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate

Treat a suspension of (cyclopropylmethyl {6-[2-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}amine (0.250 g, 0.5 mmol) in EtOH (10 mL) with tin dichloride dihydrate (0.5641 g, 2.5 mmol) and heat at reflux for 2.5 h under nitrogen. Cool to RT and quench slowly with saturated aqueous NaHCO₃ (5 mL) and EtOAc (5 mL). Add filtering agent to the resulting suspension and dilute the mixture further with 5 mL each of aqueous NaHCO₃ and EtOAc. Filter the mixture through a pad of the filtering agent. Wash the solid with 10 mL each of aqueous NaHCO₃ and EtOAc. Separate the layers and extract the aqueous phase with EtOAc (10 mL). Wash the combined organic phases with saturated aqueous NaCl (5 mL), dry with MgSO₄, filter and concentrate. Dissolve the crude phenylenediamine in EtOH (5 mL) and treat with cyanogen bromide (1.0 mmol). Quench with saturated aqueous NaHCO₃ (2 mL) and stir

for 15 – 60 min. Dilute mixture with water (5 mL) and extract with CH₂Cl₂ (2 x 10 mL). Wash the combined organic phases with saturated aqueous NaCl (5 mL), dry with MgSO₄, filter, concentrate, and purify (silica gel chromatography, eluting with a step gradient beginning with 100% CH₂Cl₂ to 5:95 5% ammonia in MeOH:CH₂Cl₂ to give the
 5 desired compound. Isolate the free base and convert it to the methanesulfonate salt by treatment of a MeOH-water solution with methanesulfonic acid followed by lyophilization.

MS (ES): m/z = 495.1 [M+H].

- 10 The compounds of EXAMPLES 16-35 may be prepared essentially as described in EXAMPLE 15.

| EXAMPLE | Compound | MS (ES): m/z [M+H]) |
|---------|---|--------------------------|
| 16 | 3-Cyclopropylmethyl-5-[2-(2,6-difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 461 |
| 17 | 5-[2-(2,6-Dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 509 |
| 18 | 5-[2-(2-Chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 475 |
| 19 | 3-Cyclopropylmethyl-5-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 443 |
| 20 | 3-Cyclopropylmethyl-5-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 476 |
| 21 | 5-[5-(2,4-Difluorophenyl)-2-(2,6-difluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 495 |
| 22 | 5-[3-(4-Fluorophenyl)-1-methylpyrazol-4-yl]-3H-3-isobutyl-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 365 |
| 23 | 5-[5-(4-Fluorophenyl)-1-methylpyrazol-4-yl]-3H-3-isobutyl-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 365 |
| 24 | 5-[3-(4-Fluorophenyl)-1-morpholinoethylpyrazol-4-yl]-3H-3-isobutyl-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 464 |
| 25 | 5-[3-(4-Fluorophenyl)-pyrazol-4-yl]-3H-3-isobutyl-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 351 |

| | | |
|----|---|-----|
| 26 | 3H-3-isobutyl-5-(3-phenyl-1-isopropylpyrazol-4-yl)-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 375 |
| 27 | 3H-3-isobutyl-5-(3-phenyl-1-methylpyrazol-4-yl)-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 347 |
| 28 | 3H-3-isobutyl-5-(3-phenyl-pyrazol-4-yl)-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 333 |
| 29 | 5-[3-(2,4-Difluorophenyl)pyrazol-4-yl]-3H-3-isobutyl-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 369 |
| 30 | 5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 445 |
| 31 | 5-[2-(2,6-Dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 491 |
| 32 | 5-[2-(2,6-Dichlorophenyl)-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 477 |
| 33 | 5-[2-(2,6-Dichlorophenyl)-5-(4-fluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 495 |
| 34 | 5-[2-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 513 |
| 35 | R-5-[2-(2-Chloro-6-fluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(1,2,2-trimethylpropyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 507 |

EXAMPLE 36

5-[2-tert-Butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5-b]pyridine methanesulfonate

- 5 Reduce and isolate {6-[2-tert-butyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine (0.43 g; 1.0 mmol) as in EXAMPLE 1. React the crude diamine with neat triethylorthoacetate at 120 °C overnight. Concentrate and dilute with 15 mL 1N HCl. Neutralize with saturated NaHCO₃ and extract with CH₂Cl₂. Wash the organic layer with saturated NaCl, dry with Na₂SO₄, concentrate, and
- 10 purify (silica gel chromatography, eluting with EtOAc:CH₂Cl₂ 50:50) to give the title compound as a tan solid (0.11 g; 53% yield). The free base product is converted to the methanesulfonate salt essentially as described in EXAMPLE 1.
- MS (ES): *m/z* = 420 [M+H].

The compounds of EXAMPLES 37-38 may be prepared essentially as described in EXAMPLE 36.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> [M+H] |
|---------|---|------------------------------|
| 37 | 5-(2- <i>tert</i> -Butyl-5-phenyl-3H-imidazol-4-yl)-3-(2,2-dimethyl-propyl)-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 402 |
| 38 | 5-[2-(2-Chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 474 |

EXAMPLE 39

- 5 5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5-*b*]pyridine methanesulfonate

Reduce {6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl}-(2,2-dimethylpropyl)amine essentially as described in EXAMPLE 16, and then react the diamine in trimethylorthoacetate as described in EXAMPLE 36 to give the free base as a tan solid (0.11 g; 49% yield). The methanesulfonate of the free base is formed essentially as described in EXAMPLE 1.

MS (ES): *m/z* = 458 [M+H].

- 15 The compounds of EXAMPLES 40-45 may be prepared essentially as described in EXAMPLE 39.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> [M+H] |
|---------|--|------------------------------|
| 40 | 5-[2-(2,6-Difluorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 476 |
| 41 | 5-[2-(2,6-Dichlorophenyl)-5-(4-fluorophenyl)-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 508 |
| 42 | 3-Cyclopropylmethyl-5-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 442 |
| 43 | 3-Cyclopropylmethyl-5-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-2-methyl-3H-imidazo[4,5- <i>b</i>]pyridine methanesulfonate | 474 |

| | | |
|----|---|-----|
| 44 | 5-(2-Cyclopropyl-5-phenyl-3H-imidazol-4-yl)-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5-b]pyridine methanesulfonate | 386 |
| 45 | 5-[2-(2,6-Dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-2-methyl-3H-imidazo[4,5-b]pyridine methanesulfonate | 490 |

EXAMPLE 46

5-
5 [2-(2-Chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridine methanesulfonate

Reduce { 6-[2-(2-chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-nitropyridin-2-yl }-(2,2-dimethylpropyl)amine essentially as described in EXAMPLE 15. React the diamine with refluxing neat triethylorthoformate for 24 h and at RT for an additional 24 h. Purify and isolate the free base essentially as described in EXAMPLE 36 (0.11 g, 49% yield). Convert to the methanesulfonate essentially as described in EXAMPLE 1.

MS (ES): m/z = 460 [M+H].

The compounds of EXAMPLE 47-48 may be prepared essentially as described in EXAMPLE 46.

| EXAMPLE | Compound | MS (ES): m/z [M+H] |
|---------|---|-------------------------|
| 47 | 5-(2-Cyclopropyl-5-phenyl-3H-imidazol-4-yl)-3-(2,2-dimethylpropyl)-3H-imidazo[4,5-b]pyridine methanesulfonate | 372 |
| 48 | 5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridine methanesulfonate | 430 |

EXAMPLE 49

5-[3-(4-Fluorophenyl)-1-isopropylpyrazol-4-yl]-3H-3-isobutylimidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate

20 Add sodium hydrosulfite (2.55 g, 14.6 mmol) to a solution of 2-isobutylamino-3-nitro-6-[3-(4-fluorophenyl)-1-isopropylpyrazol-4-yl]pyridine (0.50 g, 1.27 mmol) in 25 mL of 1:1 THF:H₂O, in the presence of NH₄OH (8.70 mL, 32% in H₂O). Dilute with water (25 mL) after 2 h. Extract with EtOAc (100 mL), dry with MgSO₄, and

concentrate. Dissolve the residue in 1:1 CH₂Cl₂:EtOH (25 mL), add cyanogen bromide (0.16 g, 1.51 mmol), and stir for about 48 h. Concentrate and purify the residue (silica gel chromatography, eluting with EtOAc:MeOH 16:1). Recrystallize from diethyl ether:hexanes to provide the free base (0.44 g, 88%). Convert to the methanesulfonate essentially as described in EXAMPLE 1 (58% yield).

5 MS (ES): m/z = 393 [M+H].

The compounds of EXAMPLE 50-62 may be prepared essentially as described in EXAMPLE 49.

| EXAMPLE | Compound | MS (ES): m/z [M+H] |
|---------|--|-------------------------|
| 50 | 5-[2- <u>tert</u> -Butyl-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 389 |
| 51 | 5-[2-(2-Fluoro-6-chlorophenyl)-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 461 |
| 52 | 5-[2-Cyclopropyl-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 373 |
| 53 | 5-[2-(2-Fluoro-6-trifluoromethylphenyl)-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 495 |
| 54 | 5-[2-(2-Fluoro-6-chlorophenyl)-5-(4-fluorophenyl-1H-imidazol-4-yl)-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 479 |
| 55 | 5-[2-isopropyl-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 375 |
| 56 | 5-[2-(2-Fluoro-6-trifluoromethylphenyl)-5-(2,4-difluorophenyl-1H-imidazol-4-yl)-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 531 |
| 57 | 5-[2- <u>tert</u> -Butyl)-5-(2,4-difluorophenyl-1H-imidazol-4-yl)-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 425 |
| 58 | 5-[2-Isopropyl)-5-(2,4-difluorophenyl-1H-imidazol-4-yl)-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 411 |
| 59 | 5-[2-(2-Fluoro-6-chlorophenyl)-5-(2,4-difluorophenyl-1H-imidazol-4-yl)-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 497 |

| | | |
|----|---|-----|
| 60 | 5-[2-Cyclopropyl]-5-(2,4-difluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 409 |
| 61 | 5-[2-Cyclopropyl]-5-(4-fluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 391 |
| 62 | 5-[2- tert -Butyl-5-(4-fluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine di-methanesulfonate | 407 |

EXAMPLE 63

N'-{5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-yl}-N,N-dimethylformamidine

Reflux N'-{5-[2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine prepared essentially as described in EXAMPLE 1 (0.10 g, 0.225 mmol), N, N-dimethylformamide dimethyl acetal (0.05 mL, 0.4 mmol) in toluene (1.5 mL) for 2 h. Cool to RT and concentrate. Purify (silica gel chromatography, eluting with 1:1 CH₂Cl₂:acetonitrile) to give the title compound (0.11 g).

MS (ES): *m/z* = 500 [M+H].

The compound of EXAMPLE 64 may be prepared essentially as described in EXAMPLE 63.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> [M+H] |
|---------|--|------------------------------|
| 64 | N'-{5-[2-(2,6-Dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-yl}-N,N-dimethylformamidine | 533 |

EXAMPLE 65

N'-{5-[2-(2,6-Dichlorophenyl)-3-methyl-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-yl}-N,N-dimethylformamidine

Stir N'-{5-[2-(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-yl}-N,N-dimethylformamidine prepared essentially as described in EXAMPLE 63 (0.10 g, 0.188 mmol), iodomethane (0.040 g, 0.282 mmol), and Cs₂CO₃ (0.09 g, 0.28 mmol) in DMF (1.5 mL) at RT for about 24 h. Extract with EtOAc and wash with water (3x), saturated aqueous NaCl, then dry over Na₂SO₄. Filter and

concentrate to give a mixture of methyl isomers. Purify (silica gel chromatography) eluting with 1:1:0.4 CH₂Cl₂:acetonitrile:hexanes to give the title compound (0.02 g). MS (ES): m/z = 548 [M+H].

5

EXAMPLE 66

5-[2-(2,6-Difluorophenyl)-3-methyl-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine

Heat N'-{5-[2-(2,6-difluorophenyl)-3-methyl-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-yl}-N,N-dimethylformamidine (0.02 g, 0.04 mol) in 10 1:1 glacial acetic acid:concentrated HCl (0.6 mL) at 100 °C for 30 min. Cool to RT. Add CH₂Cl₂ and water, neutralize with 5N NaOH to about pH = 7 with rapid stirring. Extract the aqueous phase 3x with MeCl₂, combine organic layers, wash with saturated aqueous NaCl and dry over Na₂SO₄. Filter and concentrate to give the title compound (0.02 g). MS (ES): m/z = 459 [M+H]

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The compound of EXAMPLE 67 may be prepared essentially as described in EXAMPLE 66.

| EXAMPLE | Compound | MS (ES): m/z [M+H] |
|---------|---|-------------------------|
| 67 | 5-[2-(2,6-Dichlorophenyl)-3-methyl-5-phenyl-3H-imidazol-4-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine | 493 |

EXAMPLE 68

20 3-(2,2-Dimethylpropyl)-5-(5-phenyl-3H-[1,2,3]triazol-4-yl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate

Suspend (2,2-dimethyl-propyl)-[3-nitro-6-(5-phenyl-3H-[1,2,3]triazol-4-yl)pyridin-2-yl]amine (0.180 g, 0.51 mmol), and 10% Pd/C (0.025 g) in EtOH (10 mL) and stir at RT under a balloon containing hydrogen for 5 h. Filter the reaction mixture using a filtering agent and concentrate to approximately half the reaction volume. Use the 25 diamine immediately without further isolation or purification (MS (ES): m/z 323 [M + H]), and treat with cyanogen bromide (0.09 g) in EtOH (5 mL). Stir under nitrogen for 3.5 h, quench with saturated aqueous NaHCO₃ (2.0 mL), stir, dilute with CH₂Cl₂ (5 mL) and H₂O (5 mL), and separate the phases. Extract the aqueous phase with CH₂Cl₂ (2 x 5 mL),

wash the combined organic phases with 5 mL each of H₂O and saturated aqueous NaCl, and dry with MgSO₄. Filter and concentrate. Purify the residue (silica gel chromatography, eluting with 4:96 2.0 N ammonia in MeOH:CH₂Cl₂) to give the free base. Convert to the methanesulfonate salt by treatment of a MeOH-water solution with methanesulfonic acid followed by lyophilization to give the title compound (0.07 g, 39%). MS (ES): $m/z = 348$ [M+H].

The compounds of EXAMPLE 69-72 may be prepared essentially as described in EXAMPLE 68.

| EXAMPLE | Compound | MS (ES): m/z [M+H]) |
|---------|--|--------------------------|
| 69 | 3-(2,2-Dimethylpropyl)-5-[5-(4-fluorophenyl)-3H-[1,2,3]triazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 364 |
| 70 | 3-Cyclopropylmethyl-5-[5-(4-fluorophenyl)-3H-[1,2,3]triazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 350 |
| 71 | 3-Cyclopropylmethyl-5-(5-phenyl-3H-[1,2,3]triazol-4-yl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 332 |

EXAMPLE 72

5-[2-(2-Chloro-6-fluorophenyl)-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-[1,2,3]triazolo[4,5-b]pyridine methanesulfonate

Add dropwise a solution of 6-[2-(2-chloro-6-fluorophenyl)-5-phenyl-1H-imidazol-4-yl]-N²-isobutylpyridine-2,3-diamine (1.1 g, 2.52 mmol) in CH₂Cl₂ (9 mL) and 50% aqueous AcOH (9 mL) to a solution of sodium nitrite in water (0.1 mL) (0.184 g, 2.66 mmol). Stir the reaction mixture for 15 min, add additional CH₂Cl₂ and wash the organic layer with a saturated aqueous solution of NaCl, aqueous NaHCO₃ (5%), dry with MgSO₄, and concentrate. Purify the residue (silica gel chromatography, eluting with 4:1 to 1:2 hexane:EtOAc) to give the free base (70%). MS (ES): $m/z = 447$ [M+H]. Add 0.34 mL of a 1 M solution of methanesulfonic acid in CH₂Cl₂:MeOH 9:1 to a solution of the free base (0.15 g, 0.336 mmol) in 10 mL CH₂Cl₂:MeOH 9:1. Stir the solution 5 min, concentrate, and triturate the white solid in diethyl ether. Filter the solid to provide the title compound (71%). MS (ES): $m/z = 447$ [M+H].

The compounds of EXAMPLE 73-75 may be prepared essentially as described in EXAMPLE 72.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> [M+H]) |
|---------|--|-------------------------------|
| 73 | 5-[2-(2,6-Dichlorophenyl)-5-phenyl-1H-imidazol-4-yl]-3-isobutyl-3H-[1,2,3]triazolo[4,5-b]pyridine methanesulfonate | 463 |
| 74 | 5-[2-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-[1,2,3]triazolo[4,5-b]pyridine methanesulfonate | 499 |
| 75 | 5-[2- <u>tert</u> -Butyl-5-(4-fluorophenyl)-1H-imidazol-4-yl]-3-isobutyl-3H-[1,2,3]triazolo[4,5-b]pyridine methanesulfonate | 393 |

5

EXAMPLE 76

2-Amino-5-(2-tert-butyl-5-phenyl-3H-imidazol-4-yl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide methanesulfonate

Heat a mixture of 2-amino-5-(2-oxo-2-phenylacetyl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide (0.07 g, 0.20 mmol), trimethylacetaldehyde (65 μ l, 0.6 mmol) and ammonium acetate (0.23 g, 3 mmol) in AcOH (5 mL) at 90 °C for 4 h. Cool to RT. Dilute with a saturated aqueous NaHCO₃, and extract with EtOAc. Concentrate the organic phase and purify (silica gel chromatography, eluting with 15:1 CH₂Cl₂:MeOH) to give the free base (35%). MS (ES): *m/z* = 438 [M+H]. Add 5.4 μ l of a solution 1 M methanesulfonic acid in CH₂Cl₂:MeOH 95:5 to a solution of the free base (0.02 g, 0.054 mmol) in 5 mL CH₂Cl₂:MeOH 95:5. Stir the solution 5 min, concentrate, and triturate the white solid in diethyl ether. Filter the solid to give the title compound (71%).

MS (ES): *m/z* = 438 [M+H].

20

The compounds of EXAMPLE 77-80 may be prepared essentially as described in EXAMPLE 77.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> [M+H]) |
|---------|--|-------------------------------|
| 77 | 2-Amino-5-[(2-fluoro-6-chlorophenyl)-5-phenyl-3H-imidazol-4-yl]imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide methanesulfonate | 512 |

| | | |
|----|--|-----|
| 78 | 2-Amino-5-[(2,6-dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide methanesulfonate | 528 |
| 79 | 2-Amino-5-[(2-fluoro-6-trifluoromethylphenyl)-5-phenyl-3H-imidazol-4-yl]imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide | 562 |
| 80 | 2-Amino-5-(2- <i>tert</i> -butyl-5-(2,4-difluorophenyl)-3H-imidazol-4-yl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide methanesulfonate | 476 |

EXAMPLE 81

5-[2-(2,6-Difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(propane-2-sulfonyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate

- 5 Stir a mixture of propane-2-sulfonic acid {3-amino-6-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-pyridin-2-yl} amide (0.37 g, 0.79 mmol), cyanogen bromide (0.104 g, 0.99 mmol) and lithium methoxide (0.033 g, 0.87 mmol) in methylene chloride (10 mL) for 12 h at RT. Add saturated NaHCO₃ (10 mL) and stir for 1 h. Separate the layers and extract with saturated aqueous NaCl. Dry the organic layer over NaSO₄,
 10 concentrate and purify (silica gel chromatography, eluting with a gradient of 40:60 EtOAc:hexanes to 80:20 EtOAc:hexanes) to give the free base (0.21 g, 54%). MS (ES): $m/z = 495$ [M+H]. Add methanesulfonic acid to a solution of the free base in 1 mL of a 5:1 mixture of methanol:methylene chloride. Concentrate the methanol salt solution and crystallize the salt by triturating with diethyl ether. Filter the solid, and dry to give the
 15 title compound.
 MS (ES): $m/z = 495$ [M+H].

The compounds of EXAMPLE 82-92 may be prepared essentially as described in EXAMPLE 81.

| EXAMPLE | Compound | MS (ES): m/z (M+H) |
|---------|--|-------------------------|
| 82 | 3-Butyl-5-[2-(2,6-difluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 445 |
| 83 | 3-Butyl-5-[2-(2-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine, di-methanesulfonate | 427 |

| | | |
|----|---|-----|
| 84 | 3-Butyl-5-[2-(2-chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 461 |
| 85 | 3-Butyl-5-(2- <u>tert</u> -butyl-5-phenyl-3H-imidazol-4-yl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 389 |
| 86 | 3-Butyl-5-[2-(2-fluoro-6-trifluoromethylphenyl)-5-phenyl-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 495 |
| 87 | 2-Amino-5-(5-(phenyl-2H-[1,2,3]triazol-4-yl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide | 385 |
| 88 | 5-[2-(2-Fluoro-6-trifluoromethylphenyl)-5-phenyl-3H-imidazol-4-yl]-3-(propane-2-sulfonyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 545 |
| 89 | 5-(2- <u>tert</u> -Butyl-5-phenyl-3H-imidazol-4-yl)-3-(propane-2-sulfonyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 439 |
| 90 | 5-[2-(2,6-Dichlorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(propane-2-sulfonyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 529 |
| 91 | 5-[2-(2-Chloro-6-fluorophenyl)-5-phenyl-3H-imidazol-4-yl]-3-(propane-2-sulfonyl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 511 |
| 92 | 3-Butyl-5-[2- <u>tert</u> -butyl-5-(2,4-difluorophenyl)-3H-imidazol-4-yl]-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 425 |

EXAMPLE 93

5-[2-tert-Butyl-4-(4-fluorophenyl)oxazol-5-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine

Bubble with nitrogen a suspension of 2-tert-butyl-4-(4-fluorophenyl)oxazole (0.145 g, 0.66 mmol), 5-bromo-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine (0.355 g, 1.32 mmol), cesium carbonate (6.06 g, 18.6 mmol), palladium (II) acetate (0.201 g, 10%) and triphenylphosphine (0.14 g, 0.07 mmol) in DMF (1.5 mL). Heat the reaction at 100 °C overnight, cool to RT and partition between EtOAc and saturated aqueous NaCl. Wash the organic layer with saturated aqueous NaCl. Dry with Na₂SO₄, filter, concentrate, and purify (silica gel chromatography, eluting with CH₂Cl₂:ammonia, 2 M in MeOH 50:1) to give the title compound (0.07 g, 34%).

MS (ES): *m/z* = 408 [M+H].

The compounds of EXAMPLE 94-97 may be prepared essentially as described in EXAMPLE 93, with the free base converted to the methanesulfonate essentially as described in EXAMPLE 1.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> (M+H) |
|---------|--|------------------------------|
| 94 | 5-[2- <u>tert</u> -Butyl-4-(2,4-difluorophenyl)oxazol-5-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 426 |
| 95 | 5-[4-(4-Fluorophenyl)-2-isopropoxyoxazol-5-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 394 |
| 96 | 3-Isobutyl-5-(2-methyl-4-phenylthiazol-5-yl)-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 362 |
| 97 | 5-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-ylamine methanesulfonate | 380 |

5

EXAMPLE 98

2-Amino-5-(2-tert-butyl-5-(4-fluorophenyl)oxazol-5-yl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide

Dissolve 2-amino-5-bromoimidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide (0.05 g, 0.156 mmol) in toluene (3 ml) in a sealed tube. Add 2-tert-butyl-4-(4-fluorophenyl)-5-trimethylstannanyloxazole (0.07 g, 0.17 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.02 g, 0.015 mmol). Heat the mixture at 110 °C for 4 h. Concentrate and purify (silica gel chromatography, eluting with 20:1 CH₂Cl₂:MeOH) to give the title compound. (14%).
MS (ES): *m/z* = 459 [M+H].

15

The compound in EXAMPLE 99 may be prepared essentially as described in EXAMPLE 98, with the free base converted to the methanesulfonate essentially as described in EXAMPLE 1.

| EXAMPLE | Compound | MS (ES): <i>m/z</i> (M+H) |
|---------|--|------------------------------|
| 99 | 2-Amino-5-(2-isopropyl-5-(4-fluorophenyl)oxazol-5-yl)imidazo[4,5-b]pyridine-3-sulfonic acid dimethylamide methanesulfonate | 445 |

20

Inhibition of p38 Kinase

Standard Solution Preparations

The kinase buffer solution is prepared by combining 2.5 mL 1 M Tris-HCl (pH 7.5), 0.1 mL 1 M dithiothreitol, 1.0 mL 1 M magnesium chloride, and 300 μ L 1% Triton X-100 and diluting to 100 mL with water. 84 mL of this kinase buffer solution is combined with 16 mL DMSO to prepare the 16% DMSO solution.

The 200 μ M ATP solution is prepared by adding 102.6 μ L 10 mM aqueous ATP, 25 μ L 33 P-ATP, and 163.5 μ L of 4 mM aqueous Epidermal Growth Factor Peptide 661-681 (Biomol, Catalog #P-121) in 5 mL kinase buffer solution.

The p38 kinase enzyme solution is prepared by dissolving 9.5 μ L concentrated enzyme solution (250 ng p38 enzyme/ μ L kinase buffer solution) in 1536 μ L kinase buffer solution.

Sample Preparation

An 80 μ M solution of each test compound and control compound are prepared by dissolving 2 μ L of a 10 mM stock solution of the respective compounds in dimethylsulfoxide in 248 μ L of the 16% DMSO solution in a Costar 96-well microtiter plate. The plate is placed onto the Tecan Genesis automated liquid handler for 1:3 serial dilutions.

Assay

10 μ L of serially diluted compound is placed with a Beckman Multimek 96-well automated liquid handler to the assay plate. 20 μ L of 200 μ M ATP solution is added with a Titertek Multidrop 8-channel liquid handler. 10 μ L of p38 kinase enzyme solution is transferred to the assay plate using the Multimek. The mixture is allowed to react for 40 min at 30 °C and then the reaction is stopped by adding 60 μ L of freshly prepared 5% glacial AcOH with Multidrop. 80 μ L of this solution is transferred to an "MAPH" plate using the Multimek. The plates are allowed to set for 30 min at RT and then washed/aspirated on the Titertek MAP extractor with freshly prepared 0.5% glacial AcOH (1 x 300 μ L, 2 x 200 μ L). The wells are blotted and 100 μ L MicroScint-20 scintillation

fluid (Packard Bioscience) is added with the Multidrop. The plates are allowed to sit for 30 min and counted on a PE/Wallac Microbeta Trilux scintillation counter for ^{33}P -isotope.

All exemplified compounds were initially tested at 10 concentrations (20 μM – 1 nM using 1:3 serial dilutions). Compounds with IC_{50} values less than 25 nM were re-
5 tested at a starting concentration of 2 μM to 0.1 nM (1:3 serial dilutions). IC_{50} values were calculated (IDBS ActivityBase software) for each compound using non-linear regression. All exemplified compounds were tested essentially as described above and were found to inhibit the p38 kinase enzyme with an IC_{50} of at least 5 μM .

10 Inhibition of TNF- α *in vitro*

Mouse Peritoneal Macrophages

1 mL thioglycolate broth (5.0 g yeast extract, 15.0 g caseitone or trypticase, 5.0 g dextrose, 2.5 g sodium chloride, 0.75 g L-cystine, 0.5 g sodium thioglycolate, 1.0 mg resazurin, and 0.75 g agar in 1.0 L distilled water) are injected into the peritoneal cavity of
15 Balb/C female mice. At day 4 or 5 post-injection the mice are sacrificed and then injected i.p. with 4 mL RPMI-1640 medium (BioWhittaker) and the peritoneal macrophages are withdrawn by syringe.

Cytokine Production

20 Mouse peritoneal macrophages are counted with a hemocytometer and adjusted to 5×10^5 cells/well in 96-well plates in RPMI-1640 medium with 10% fetal bovine serum. 200 μL /well is plated in 96-well plates and the cells allowed to settle and adhere to the bottom of the well for at least 3 h. The test compound or standard p38 kinase inhibitor is pre-treated using a series of 8 concentrations for 1 h at 37 $^{\circ}\text{C}$ (20 μL /well). The cells are
25 treated with a mixture of 50 ng/mL lipopolysaccharide (LPS) and 10 U/mL interferon- γ for 18 h at 37 $^{\circ}\text{C}$ (20 μL /well). The conditioned media is harvested and assayed for TNF- α production using the Luminex procedure.

TNF- α /Luminex Detection Assay (Bio-Rad Bio-Plex Kit – Catalog #171-G12221)

30 The lyophilized premixed TNF- α standard (1 standard tube/ two 96-well plates) is reconstituted with 50 μL sterile water (500,000 pg/mL). The samples are vortexed for

5 seconds, incubated on ice for 30 min, and vortexed for 5 seconds before use. A set of twelve 1.5 mL tubes are labeled with #1-thru #12 and then the amounts of cell media shown below added to the appropriate tubes (standard concentrations are as follows: 50,000; 25,000; 12,500; 6,250; 3,125; 1,562.5; 781.3; 390.6; 195.3; 97.7; 48.8; and 24.4 pg/mL). The premixed anti-cytokine conjugated beads are vortexed (25X) vigorously for 30 seconds. The anti-cytokine conjugated beads are diluted to a 1X concentration using 1X Bio-Plex Assay Buffer. For every plate, 240 μ L of the pre-mixed beads is added to 5760 μ L of Bio-Plex Assay Buffer. A Millipore 96-well filter plate is blocked with 100 μ L/well of blocking buffer. The blocking buffer is filtered through using a Millipore filtration system and then toweled dry. 2 washes are performed on the filter plate with 100 μ L/well of Bio-Plex Assay Buffer and toweled dry. The 1X anti-cytokine conjugated beads are vortexed for 15 seconds and added 50 μ L to each well. This is filtered through and toweled dry. 2 washes are performed on plates with 100 μ L/well of Bio-Plex Wash Buffer. Again, it is filtered through and toweled dry.

50 μ L of sample or standard is added to each sample well. This is incubated for 60 seconds at RT on a shaker protected from light at setting 6 and then for 30 min at setting 3 and then placed in the refrigerator overnight. 3 washes are performed with Bio-Plex Wash Buffer. Filter through and toweled dry. The cytokine detection antibody is prepared (~10 min prior to use) for every plate and 60 μ L of the premixed cytokine detection antibody stock is added to 5940 μ L of Bio-Plex Detection Antibody Diluent. 50 μ L of cytokine detection antibody is added and incubated for 60 seconds at RT on a shaker protected from light at setting 6 and then for 30 min at setting 3.3 washes are performed with the Bio-Plex Wash Buffer. This is filtered through and toweled dry. Strept-PE (~10 minutes prior to use) is prepared for every plate and 60 μ L to 5940 μ L of Bio-Plex Assay Buffer added. 50 μ L of Streptavidin-PE is added to each well and incubated for 60 seconds at RT on a shaker protected from light at setting 6 and then for 10 min at setting 3. 3 washes are performed with Bio-Plex Wash Buffer. This is filtered through. The beads are re-suspended in 100 μ L/well of Bio-Plex Assay Buffer. Standards and samples are read on a Luminex machine. These intensity readings are then converted to picogram/milliliter units based on a 12-point standard curve created in

duplicate using a four-parameter logistic regression method (Bio-Plex Manager 2.0, Bio-Rad), and the IC₅₀ calculated.

Representative members of the exemplified compounds were tested essentially as described above and suppressed TNF- α *in vitro* with an IC₅₀ less than 100 nM.

5

Inhibition of TNF- α *in vivo*

Compounds are administered p.o. (100, 30, 10 and 3 mg/kg) to female Balb/c mice (5 mice/dose). After 2 h, lipopolysaccharide (LPS, E. coli serotype 0111:B4, 5 mg/kg) is administered i.v. in the tail vein of each mouse. One hour after LPS administration the mice are asphyxiated by CO₂ inhalation and bled out via cardiac puncture.

10

TNF- α /Luminex Detection Assay (Bio-Rad Bio-Plex Kit – Catalog #171-G12221)

Reconstitute the lyophilized premixed TNF- α standard (1 standard tube/ two 96-well plates) with 50 μ L sterile water (500,000 pg/mL). Gently vortex for 5 seconds, incubate on ice for 30 min, and vortex for 5 seconds before use. Label a set of twelve 1.5 mL tubes with #1-thru #12 and then add the amounts of cell media shown below to the appropriate tubes (standard concentrations are as follows: 50,000; 25,000; 12,500; 6,250; 3,125; 1,562.5; 781.3; 390.6; 195.3; 97.7; 48.8; and 24.4 pg/mL). Vortex the premixed anti-cytokine conjugated beads (25X) vigorously for 30 seconds. Dilute the anti-cytokine conjugated beads to a 1X concentration using 1X Bio-Plex Assay Buffer. For every plate, add 240 μ L of the pre-mixed beads to 5760 μ L of Bio-Plex Assay Buffer. Block a Millipore 96-well filter plate with 100 μ L/well of blocking buffer. Filter through the blocking buffer using a Millipore filtration system. Towel dry. Perform 2 washes on the filter plate with 100 μ L/well of Bio-Plex Assay Buffer and towel dry. Vortex the 1X anti-cytokine conjugated beads for 15 seconds and add 50 μ L to each well. Filter through and towel dry. Perform 2 washes on plates with 100 μ L/well of Bio-Plex Wash Buffer. Filter thru and towel dry. Add 25 μ L of serum sample and 25 μ L of diluent (Bio-Rad) or 50 μ L standard to each sample well. Incubate for 60 seconds at RT on a shaker protected from light at setting 6 and then for 30 min at setting 3 and then place in the refrigerator overnight. Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry.

25

30

Prepare cytokine detection antibody (~10 min prior to use) for every plate, add 60 μ L of the premixed cytokine detection antibody stock to 5940 μ L of Bio-Plex Detection Antibody Diluent. Add 50 μ L of cytokine detection antibody and incubate for 60 seconds at RT on a shaker protected from light at setting 6 and then for 30 min at setting 3.

- 5 Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry. Prepare strept-PE (~10 minutes prior to use) for every plate, add 60 μ L to 5940 μ L of Bio-Plex Assay Buffer. Add 50 μ L of Streptavidin-PE to each well and incubate for 60 seconds at RT on a shaker protected from light at setting 6 and then for 10 min at setting 3. Perform 3 washes with Bio-Plex Wash Buffer. Filter through. Re-suspend the beads in
- 10 100 μ L/well of Bio-Plex Assay Buffer. Read standards and samples on Luminex machine. These intensity readings are then converted to picogram/milliliter units based on a 12-point standard curve created in duplicate using a four-parameter logistic regression method (Bio-Plex Manager 2.0, Bio-Rad), and the IC₅₀ calculated.

- Representative members of the exemplified compounds were tested essentially as
- 15 described above and suppressed TNF- α *in vivo* with an IC₅₀ less than 100 mg/kg.

Effect on Intra-articular LPS induced TNF- α

- Intra-articular injection of LPS into rat ankles induces the synthesis of TNF- α , which can be measured in synovial lavage fluid. High levels of TNF- α are detectable
- 20 within 2 hours. Since the joint is the site where arthritis develops, this model can rapidly determine whether an orally administered compound has an effect on an inflammatory response in the synovium.

- Six female Lewis rats (150-200 g) are placed in each treatment group. The animals are given vehicle (1% NaCarboxymethylcellulose-0.25% Tween 80) or test compound
- 25 (1 mg/kg, 3mg/kg, 10mg/kg, and 30mg/kg) orally. One hour later, 10 μ L LPS (10 μ g) is administered intra-articularly into the right ankle of each rat, while the left ankle receives 10 μ L of saline. After two hours, each ankle is lavaged with 100 μ L of saline. The lavage is collected and stored at -80 $^{\circ}$ C.

- 30 Group#1: Vehicle (1%NaCMC-0.25%Tween 80, 1 mL, PO)
Group#2: Test compound (1 mg/kg, 1 mL, PO)

Group#3: Test compound (3 mg/kg, 1 mL, PO)

Group#4: Test compound (10 mg/kg, 1 mL, PO)

Group#5: Test compound (30 mg/kg, 1 mL, PO)

5 TNF- α is measured with a commercially available ELISA kit (R&D, RTA00).

Treatment with Example 78 produced a dose-dependent inhibition of TNF- α synthesis, as measured in the synovial lavage fluid.

B16F10 Melanoma Target (MAPKAP-K2 Phosphorylation) and B16F10 Melanoma

10 Metastasis Efficacy Model

Inhibition of B16F10 Melanoma Lung Metastases

The B16F10 melanoma cell line is obtained from the American Type Culture Collection, Rockville, MD. The cells are cultured in RPMI-1640 medium supplemented with 10% fetal calf serum. The cells grown *in vitro* are harvested during their exponential growth phase by gentle trypsinization, washed twice in medium, and resuspended in serum-free RPMI-1640 medium. The number of monodisperse viable cells is determined using a hemocytometer and adjusted to 1×10^6 cells/mL. Tumor cells are injected intravenously into the tail vein of normal C57Bl6 mice with an inoculum volume of 0.2 mL containing 200,000 cells. Mice are treated with test compound or vehicle control starting 1 day before i.v. tumor inoculation. The test compound is prepared as a suspension formulation in 1% NaCMC/0.25% polysorbate 80 and probe sonicated in an injection volume of 1% body weight (e.g., the 30 mg/kg dose level is prepared at 3 mg/mL and 0.2 cc was administered per 20 g mouse). Mice are treated orally tid. with the test compound at 30, 10, and 3 mg/kg (90, 30, and 9 mg/kg/day) from days -1 thru 16 after tumor cell inoculation. Control mice receive the vehicle alone in an identical manner. On day 16, the mice are sacrificed, and the lungs are harvested and fixed in 3% paraformaldehyde. Lung lesions are quantitated by manual counting under a dissecting microscope.

30 B16F10 target (phosphorylated MAPKAPK-2) Studies

The B16F10 melanoma cell line is obtained from the American Type Culture Collection, Rockville, MD. The cells are cultured in RPMI-1640 medium supplemented

with 10% fetal calf serum. The cells grown *in vitro* are harvested during their exponential growth phase by gentle trypsinization, washed twice in medium, and resuspended in serum-free RPMI-1640 medium. The number of viable cells is determined using a hemocytometer and adjusted to 1×10^7 /mL. Tumor cells are injected subcutaneously in normal C57Bl6 mice. Inoculum volume per mouse is 0.2 mL (2,000,000 cells). When the tumors reach 300-500 mg, the mice are used for target inhibition studies at either a fixed time (2.5 hours) after p.o. compound treatment or pharmacodynamic studies where the tumors are collected at multiple time-points (e.g., 3, 6, 9, 12, 15, and 18 h) after p.o. compound treatment.

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Protein Extraction and Immuno-Blot Analysis

Tumors collected as described above are immediately snap-frozen in liquid nitrogen and stored at -80°C . Tumor tissues are homogenized on ice using a Daunce homogenizer in an extraction buffer (25 mM Tris pH 7.5 containing the following protease inhibitors: 10 $\mu\text{g}/\text{mL}$ leupeptin, 10 $\mu\text{g}/\text{mL}$ soybean tryp-chymotrypsin inhibitor, 10 $\mu\text{g}/\text{mL}$ N-tosyl-L-phenylalanine chloromethyl ketone, 10 $\mu\text{g}/\text{mL}$ aprotinin, N α -p-tosyl-L- arginine methyl ester, 7 mM benzamidine, 0.3 mM phenylmethylsulfonyl fluoride and two tablets of Roche complete protease inhibitor cocktail; following phosphatase inhibitors: 60 mM beta-glycerophosphate, 1 mM sodium vanadate, 10 mM sodium fluoride. 20 mM p-nitrophenyl phosphate, 1 μM okadaic acid, 1 μM microcystin, 2.5 mM sodium pyrophosphate; and 1 mM dithiothreitol, 15 mM EDTA, 5 mM EGTA, 1% Triton X100 and 150 mM NaCl). Tissue lysates are cleared by centrifugation in a refrigerated microcentrifuge at 14,000 rpm and at 1°C for 20 min. Supernatants are transferred to fresh microfuge tubes prechilled on ice and snap-freeze again in liquid nitrogen or dry ice. After quick thaw to about 80% completion in lukewarm water, the samples are placed on ice to complete thaw. The samples are centrifuged again at 14,000 rpm and at 1°C for 15 min. The supernatant is transferred to fresh prechilled microfuge tubes and protein concentrations are measured using Bio-Rad protein assay reagents using bovine serum albumin as protein standard.

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Protein extracts are equalized with the extraction buffer. An equal volume of 2X SDS sample buffer is added to the protein extracts and boiled in a waterbath for 5

min. 100 µg of protein extract per sample is used for electrophoresis on 4-20% gradient SDS-PAGE gel and transferred onto nitrocellulose (NC) membranes. NC membranes are blocked in 5% BSA in TBST (20 mM Tris pH = 7.5, 500 mM NaCl, 0.05% Tween 20 and 0.02% sodium azide) for least 1 h. The membranes are then
5 incubated in primary antibody at 1:1,000 with 5% BSA in TBST overnight on a shaker with 80 rpm at 4 °C. Membranes are washed 4 X, 10 min each, with TBST. The membranes are then incubated for 40 min with secondary antibody HRP (horse radish peroxidase) conjugate at 1:10,000 dilution in 3% non-fat milk in TBST and washed again 4 times with TBST, 10 min each. The immuno-blots are then visualized
10 by enhanced chemiluminescence (ECL, Amersham) as per manufacturer's instructions. All primary antibodies are purchased from Cell Signaling and secondary antibody HRP conjugates are obtained from Amersham. Gels, membranes and apparatus used for electrophoresis and Western blotting are purchased from Invitrogen. Protein bands of interest are quantified from films using Kodak Image
15 Station 1000.

P815 Tumor Model

Female (6-8 weeks old) DBA/2 mice (Taconic) are implanted subcutaneously into the hind flank region on day 0 with P815 cells (0.5×10^6 cells in 200 µl of RPMI 1640).
20 P815 tumor cells are purchased from ATCC and are cultured in RPMI 1640 medium, supplemented with glutamine and 10% bovine serum at 37 °C in 5% CO₂ cell culture incubator. Tumor-bearing animals are treated with oral administration of test compound at different doses or vehicle with frequency of three times a day started on the day of implantation. Tumor growth is monitored every 2 days by measuring perpendicular
25 diameters. Tumor volume expressed in milligram (mg) is determined as the product of the largest diameter (a) and its perpendicular (b) according to the formula [tumor volume = $a \times b^2 \times 0.536$].

In Vivo Target Inhibition Study in P815 Mastocytoma Model

30 *In vivo* target inhibition is determined by measuring the effect of inhibitor treatment on the phosphorylation of MAPKAP-K2 expressed in P815 tumor tissues. Tumors in DBA/2 mice received P815 cells subcutaneous implantation are allowed to

grow to a size of 300-500 mg without treatment. Tumor bearing mice are then given oral administration of test compound or vehicle. To investigate time course related target inhibition by test compound, tumors are harvested from CO₂ sacrificed animals at the indicated times (3 h, 6 h, 12 h, and 18 h) after compound is dosed at 30 mg/kg. Dose-dependent target inhibition by test compound is investigated by harvesting tumors at 3 h after orally given different doses of test compound or vehicle. Harvested tumors are immediately snap frozen onto dry ice, pulverized, homogenized and lysed in cooled lysis buffer containing proteinase and phosphatase inhibitors. After centrifugation to remove cell debris, supernatants containing 100 microgram total proteins are resuspended in 2 x Tris-Glycin loading buffer and subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (10% Tris-Glycine) under reducing conditions. Proteins are subsequently blotted onto a PDVF membrane and were then blocked in 5% milk PBS containing 0.1% Tween-20 for 1 h at RT. The membrane is then incubated with primary antibody (anti-phospho-MAPKAP-K2, Cell Signaling) at 4 °C overnight followed by incubation with secondary antibody (anti-rabbit HRP-conjugated IgG) at room temperature 1 h. Phospho-MAPKAP-K2 expression level is visualized by Phospho-Image detection system after the enhanced chemiluminescence (ECL) detection is used to reflect the presence of proteins on the PVDF blots. Expression level of phospho-p38 MAP kinase and total p-38 MAP kinase is also monitored by similar western blotting procedure.

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Rat Collagen Induced Arthritis Efficacy Model

Female Lewis rats (\approx 190 g, Charles River Labs) are immunized with Bovine type II collagen (2 mg/mL) emulsified with an equal volume of adjuvant (aluminum hydroxide). were used. The rats are immunized with approximately 0.3 mg of the emulsion intradermally on the back near the base of the tail. All animals are re-immunized 7 days later according to the same protocol. The rats begin to develop arthritis (characterized by swelling and redness of one or both ankles) from 12 to 14 days after the first immunization. The rats are equally distributed into five treatment groups at the first signs of arthritis and treatment is initiated with each rat dosed bid for 14 days.

30 Treatment groups:

Group 1 Vehicle (1% NaCarboxymethylcellulose+0.25% Tween 80) 1 mL, PO,
 Bid x 14 days

| | |
|---------|--|
| Group 2 | Test compound, 5 mg/kg, 1 mL, PO, Bid x14 |
| Group 3 | Test compound, 15 mg/kg, 1 mL, PO, Bid x14 |
| Group 4 | Test compound, 30 mg/kg, 1 mL, PO, Bid x14 |
| Group 5 | Prednisolone 10 mg/kg, 1 mL, PO, qd x14 |

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Ankle diameter is measured with calipers 5 days a week and recorded. Data is expressed as the area under the curve (AUC) generated from the composite inflammation scores and statistical analysis performed.

Oral administration of the compounds of the present invention is preferred.

10 However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula I may also be administered by the percutaneous, intramuscular, 15 intranasal or intrarectal route in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

20 The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the 25 like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing 30 gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be

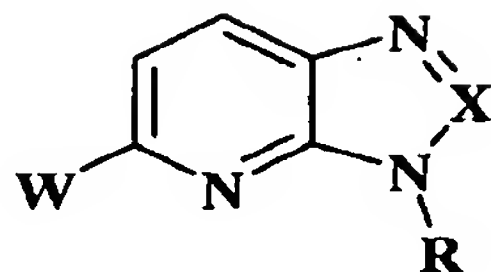
obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate, disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like; lubricants such as: magnesium stearate, stearic acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate and polysorbate 80; and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, hydroxypropyl methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

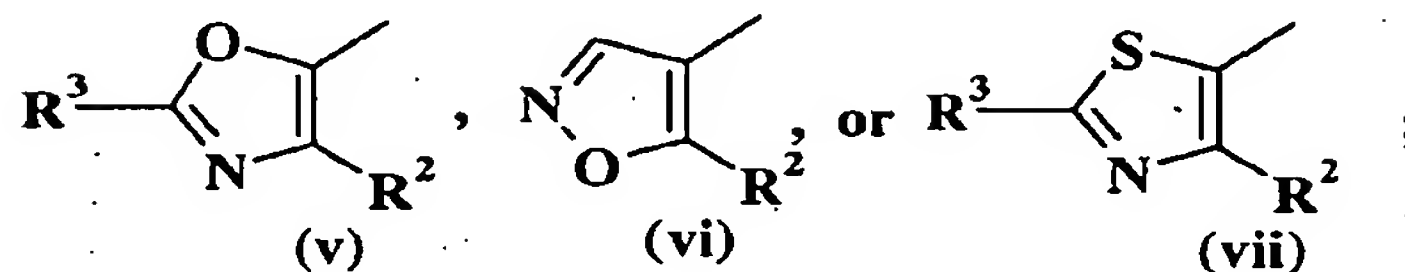
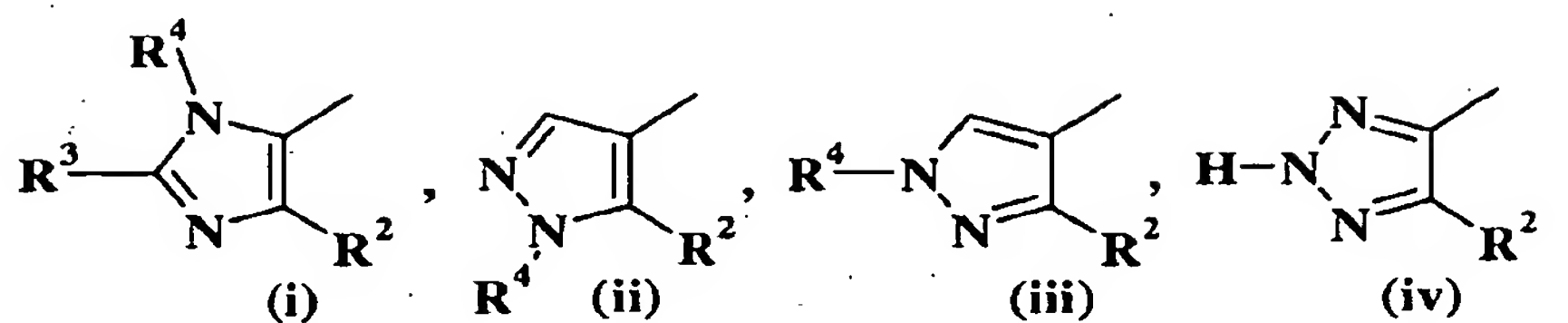
WE CLAIM:

1. A compound of Formula I:



I

5 where:



W is

X is N, or C-R¹;

R is C₁-C₇ alkyl, C₃-C₇ cycloalkyl, (C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl), -SO₂-(C₁-C₇ alkyl), or -SO₂-NR⁵R⁶;

10 R¹ is hydrogen, amino, methyl, or -N=CH(NMe)₂;

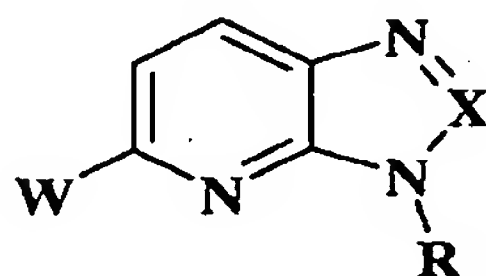
R² is phenyl optionally substituted with one or two substituents independently selected from halo;

R³ is hydrogen, C₁-C₇ alkyl, C₃-C₇ cycloalkyl, or phenyl optionally substituted with one or two substituents independently selected from halo and trifluoromethyl;

15 R⁴ is hydrogen or C₁-C₇ alkyl;

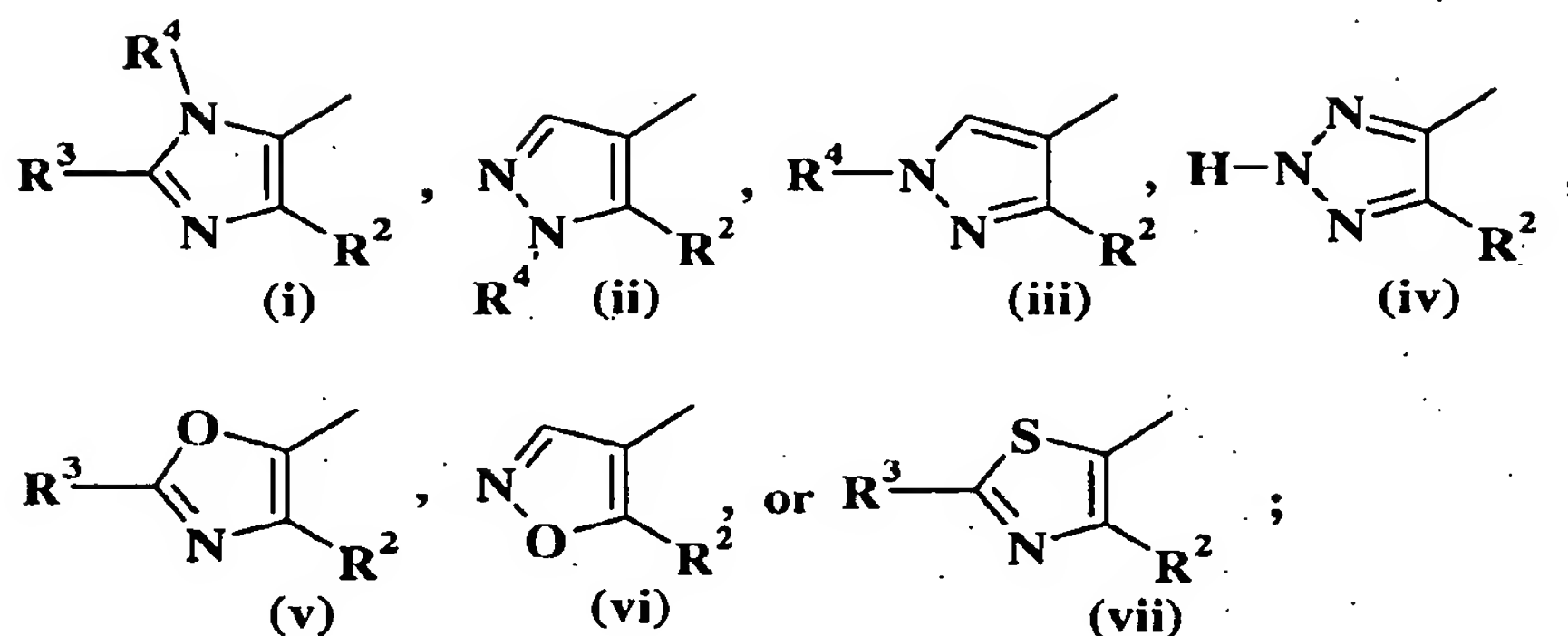
R⁵ and R⁶ are independently selected from the group consisting of C₁-C₇ alkyl; or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical formulation comprising a compound of Formula I:



I

5 where:



W is

X is N, or C-R¹;

R is C₁-C₇ alkyl, C₃-C₇ cycloalkyl, (C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl), -SO₂-(C₁-C₇ alkyl), or -SO₂-NR⁵R⁶;

10 R¹ is hydrogen, amino, methyl, or -N=CH(NMe)₂;

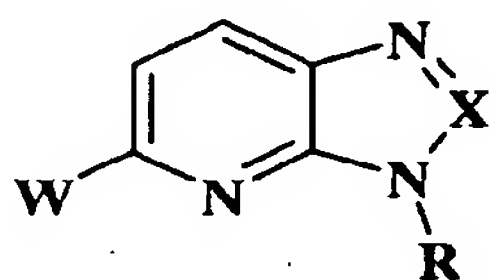
R² is phenyl optionally substituted with one or two substituents independently selected from halo;

R³ is hydrogen, C₁-C₇ alkyl, C₃-C₇ cycloalkyl, or phenyl optionally substituted with one or two substituents independently selected from halo and trifluoromethyl;

15 R⁴ is hydrogen or C₁-C₇ alkyl;

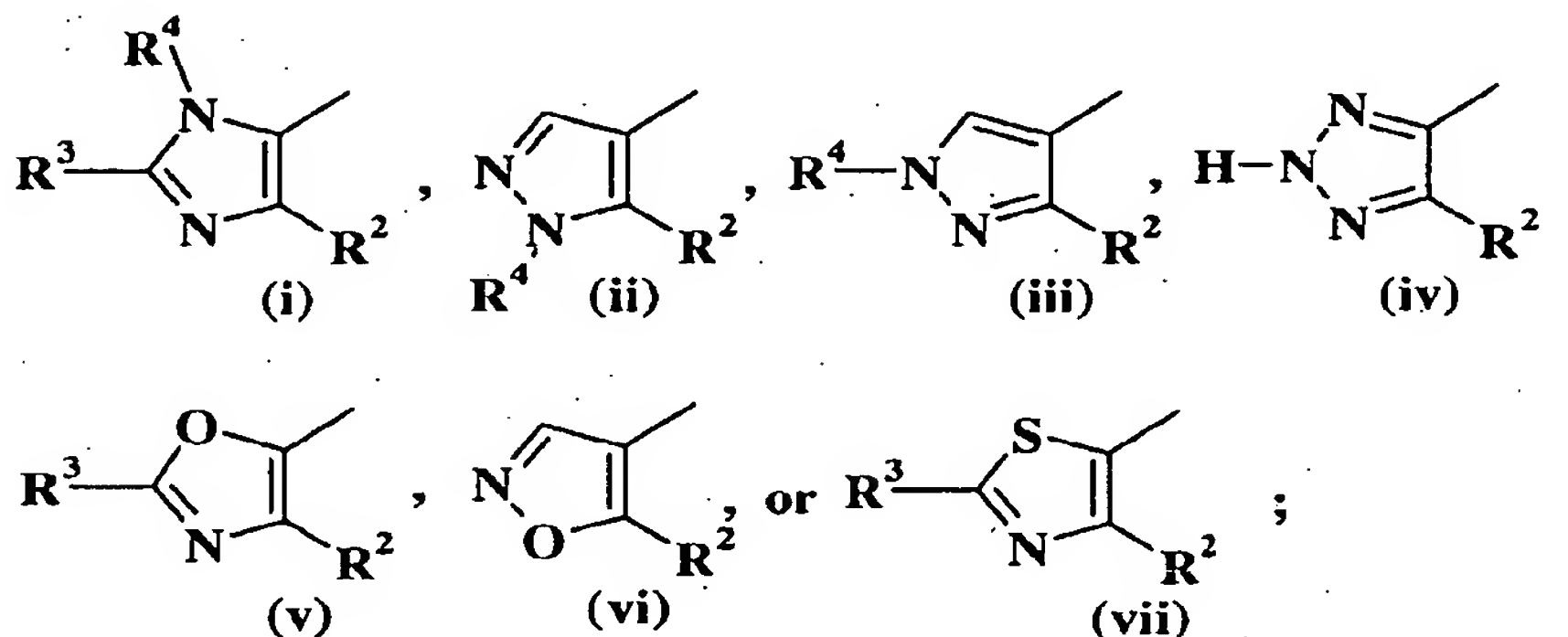
R⁵ and R⁶ are independently selected from the group consisting of C₁-C₇ alkyl; or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

3. A method of inhibiting p-38 kinase in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I:



I

where:



W is

X is N, or C-R¹;

R is C₁-C₇ alkyl, C₃-C₇ cycloalkyl, (C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl), -SO₂-(C₁-C₇ alkyl), or -SO₂-NR⁵R⁶;

R¹ is hydrogen, amino, methyl, or -N=CH(NMe)₂;

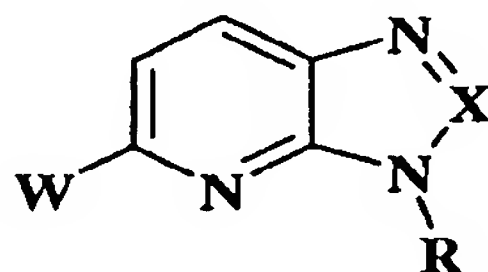
R² is phenyl optionally substituted with one or two substituents independently selected from halo;

R³ is hydrogen, C₁-C₇ alkyl, C₃-C₇ cycloalkyl, or phenyl optionally substituted with one or two substituents independently selected from halo and trifluoromethyl;

R⁴ is hydrogen or C₁-C₇ alkyl;

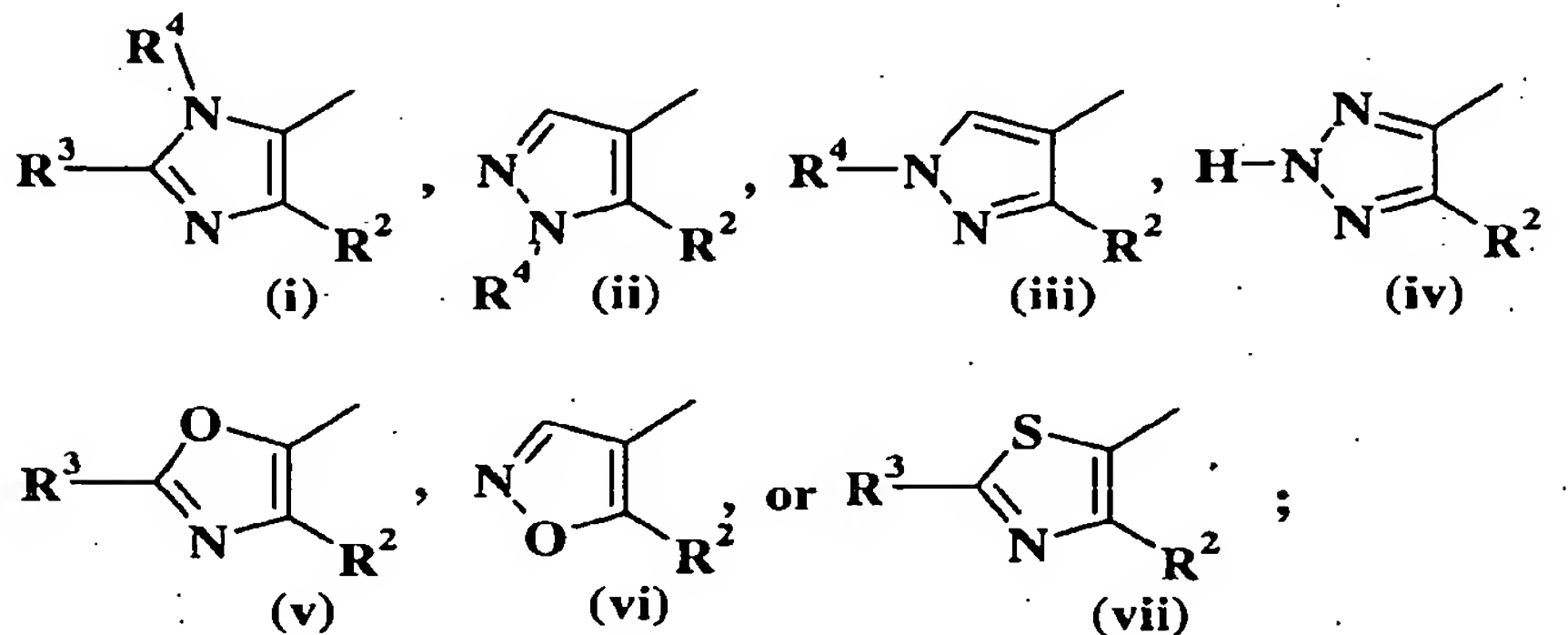
R⁵ and R⁶ are independently selected from the group consisting of C₁-C₇ alkyl; or a pharmaceutically acceptable salt thereof.

4. A method of treating conditions resulting from excessive cytokine production in a mammal comprising administering to a mammal in need of such treatment a cytokine-suppressing amount of a compound of Formula I



I

where:



W is

X is N, or C-R¹;

R is C₁-C₇ alkyl, C₃-C₇ cycloalkyl, (C₁-C₇ alkylene)-(C₃-C₇ cycloalkyl), -SO₂-(C₁-C₇ alkyl), or -SO₂-NR⁵R⁶;

R¹ is hydrogen, amino, methyl, or -N=CH(NMe)₂;

R² is phenyl optionally substituted with one or two substituents independently selected from halo;

R³ is hydrogen, C₁-C₇ alkyl, C₃-C₇ cycloalkyl, or phenyl optionally substituted with one or two substituents independently selected from halo and trifluoromethyl;

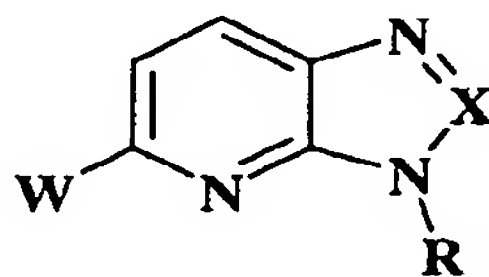
R⁴ is hydrogen or C₁-C₇ alkyl;

R⁵ and R⁶ are independently selected from the group consisting of C₁-C₇ alkyl; or a pharmaceutically acceptable salt thereof.

5. A method of Claim 4, where the cytokine is tumor necrosis factor α .

ABSTRACT

The present invention provides kinase inhibitors of Formula I:



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